CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-846

MICROBIOLOGY REVIEW(S)

DF-N-20-846

APR 17 1998

REVIEW FOR HFD-540

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review # 2 of NDA 20-846
April 15, 1998

A. 1. **APPLICATION NUMBER:** NDA 20-846

APPLICANT: Novartis
59 Route 10
East Hanover, NJ 07936-1080

2. **PRODUCT NAME:** Lamisil® DermGel™

3. **DOSAGE FORM:** Terbinafine emulsion gel (1%) topical.

4. **METHOD OF STERILIZATION:** None

5. **PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION:** Terbinafine is an antifungal and the proposed indication for the drug product is for the topical treatment of pityriasis due to *Malassezia furfur*, and tinea infections..

6. **DRUG PRIORITY CLASSIFICATION:** S

B. 1. **DATE OF INITIAL SUBMISSION:** April 29, 1997

2. **DATE OF AMENDMENT:** <u>April 3, 1998</u>

3. **DATE OF CONSULT:** May 12, 1997 April 7, 1998

4. **RELATED DOCUMENTS:** (none)

5. **ASSIGNED FOR REVIEW:** May 15, 1997 April 13, 1998

C. **REMARKS:** Lamisil® DermGel™ is the third formulation of Lamisil that has been developed by Novartis. Lamisil Cream 1% (NDA 20-192) was approved on 12/30/92, and Lamisil Solution 1% (NDA 20-749) was submitted to the FDA on 10/16/96.

Microbiologist's Review #1 yielded two deficiencies which were forwarded (via FAX) to the applicant on March 5, 1998. The applicant's corresponding responses to these deficiencies are the subject of this review.

D. CONCLUSIONS:

The application is recommended for approval for issues concerning microbiology drug product quality. Specific comments are provided in section "E. REVIEW NOTES".

/S/

4/15/98

Neal Sweeney, Ph.D.

PTK 4/17/98

cc:

Original NDA 20-846
HFD-540/ Division File
HFD-540/CSO/R.Blay/S. Kummerer
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, April 15, 1998
R/D initialed by P. Cooney, April 15, 1998

Blaj 540

OCT 17 1997

REVIEW FOR HFD-540

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review # 1 of NDA 20-846
October 16, 1997

A. 1. **APPLICATION NUMBER:** NDA 20-846

APPLICANT: Novartis
59 Route 10
East Hanover, NJ 07936-1080

2. **PRODUCT NAME:** Lamisil® DermGel™

3. **DOSAGE FORM:** Terbinafine emulsion gel (1%) topical.

4. **METHOD OF STERILIZATION:** None

5. **PHARMACOLOGICAL CATAGORY and/or PRINCIPLE INDICATION:** Terbinafine is an antifungal and the proposed indication for the drug product is for the topical treatment of pityriasis due to *Malassezia furfur*, and tinea infections..

6. **DRUG PRIORITY CLASSIFICATION:** S

B. 1. **DATE OF INITIAL SUBMISSION:** April 29, 1997

2. **DATE OF CONSULT:** May 12, 1997

3. **RELATED DOCUMENTS:** (none)

4. **ASSIGNED FOR REVIEW:** May 15, 1997

C. **REMARKS:** Lamisil® DermGel™ is the third formulation of Lamisil that has been developed by Novartis. Lamisil Cream 1% (NDA 20-192) was approved on 12/30/92, and Lamisil Solution 1% (NDA 20-749) was submitted to the FDA on 10/16/96.

D. CONCLUSIONS:

The application is approvable for issues concerning drug product microbial limits and preservative effectiveness testing, provided the applicant commit to include both preservative effectiveness and microbial limits testing in the stability commitment protocol. Additionally preservative effectiveness acceptance criteria should be part of the drug product specification.

/S/

10/16/97

Neal Sweeney, Ph.D. date 10/17/97

cc:

Original NDA 20-846
HFD-540/ Division File
HFD-540/CSO/R.Blay
HFD-805/Consult File/N. Sweeney

Drafted by: Neal Sweeney, October 16, 1997
R/D initialed by P. Cooney, October 16, 1997

FEB 2 1998

Consultative Review for HFD-540
Division of Topical Drug Products
Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review #1

Requester:	Susan Kummerer, CSO HFD-540
Date of Request:	11-20-97
Reason for Request:	Clinical Microbiology Review of antifungal activity
IND/NDA Number:	NDA # 20-846
Review Date:	1-16-98
Submission/Type:	Original NDA
Document Date:	4-29-97
CDER Date:	4-29-97
Assigned Date:	11-25-97
Applicant:	Novartis Pharmaceuticals Corp. Drug Regulatory Affairs 59 Route 10 East Hanover, NJ 07936-1080
Contact Person:	Patricia McGovern, Assistant Director Drug Regulatory Affairs 59 Route 10 East Hanover, NJ 07936 Phone: (973) 503-7384

Drug Product Name:

Proprietary:	Lamisil® DermGel™
Nonproprietary/USAN:	Terbinafine emulsion gel
Code Names/#'s:	None
Chemical Type:	Allylamine derivative
Therapeutic Class:	3S

ANDA Suitability Petition/DESI/Patent Status:
Not Applicable

Pharmacological Category/Indication:
Antifungal—Allylamine derivative/Topical treatment of Tinea pedis, tinea cruris, or tinea corporis due to *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum,* and pityriasis versicolor due to *Malassezia furfur*

Dosage Form:	DermGel
Strength(s):	1%
Route of Administration:	Topical
Dispensed:	__X__ Rx ____ OTC

Supporting Documents:
DMF:
NDA: 20192, 20539
IND:

REMARKS/COMMENTS:

This microbiological review is concerned with only the clinical aspects of this applications [mechanism of action, *in-vitro* activity, *in-vivo* animal models]. The microbiological aspects of the manufacturing controls for this product are reviewed by a different consulting division.

This NDA is for a product which includes an active ingredient previously approved by FDA for drug use. The ingredient is an allylamine derivative, terbinafine, with antifungal activity. Its antifungal activity is derived from inhibition of squalene epoxidase, a key enzyme in ergosterol biosynthesis. The antifungal activity of terbinafine is related to the corresponding accumulation of squalene within the fungal cell wall.

The applicant is seeking approval for a new formulation, Lamisil® DermGel™(each gram contains 10 mg of terbinafine in an emulsion gel), to be used in topical treatment of pityriasis versicolor due to *Malassezia furfur, and* tinea pedis, tinea cruris, or tinea corporis, due to *Trichophyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum.*

1. CLINICAL STUDIES

The efficacy and safety of Lamisil 1% emulsion gel is being supported by five clinical trials in four indications. Table 1 lists these five studies. All five are considered pivotal and placebo controlled studies.

TABLE 1. List of pivotal studies in claimed indications.

Indication	Study[a]	Location	Duration of Treatment	Follow-up Period	No. of Subjects Enrolled: Enrolled	Lamisil 1% (3%)	Placebo	Enrolled Subjects: Age Range (Mean)	Sex %M %F
Pityriasis versicolor	SFG 203	Sweden	1 wk OD	7 wks	61	31	30	[redacted] (36.8)	50.8 49.2
	SFG 302	Norway/ Sweden	1 wk OD	7 wks	129	87	42	[redacted] (36.0)	51.0 48.1
Tinea pedis	SFG 102	UK	5 days OD	37 days	85	30 (28)	27	[redacted] (39.8)	69.4 30.6
	SFG 202	Finland/ Belgium	1 wk OD	7 wks	101	51	50	[redacted] (43.3)	66.3 33.7
Tinea Corporis/ Cruris	SFG 201	South Africa	1 wk OD	7 wks	83	40	43	[redacted] (37.9)	78.3 21.7

[a] All studies are placebo-controlled, randomized, double-blind, parallel group, multicenter in design

All five studies follow similar study designs and subject inclusion criteria. The protocols required that each subject have a clinical diagnosis of the study indication. In all indications this was to be confirmed by positive mycology (positive microscopy, confirmed by positive culture in all indications except pityriasis versicolor). On the basis of positive microscopy results, treatment could be initiated. The mycological examinations were performed on a target lesion which was identified at the screening visit and consistently evaluated, both mycologically and clinically, throughout the study. All visible lesions were treated. The efficacy was measured by assessment of clinical signs and symptoms, mycological results and overall assessment of efficacy by the investigator. A total of 459 patients were enrolled. Of these, 267 were randomized to Lamisil and 192 to placebo. This resulted in a total of 453 subjects for safety analysis: 262 Lamisil subjects and 191 placebo subjects.

In the pityriasis versicolor studies, the criteria for Effective Treatment were met if, at the same evaluation, a subject had both negative microscopy and a Total Signs and Symptoms Score(TSSS = sum of scores for individual signs and symptoms) of 0 or 1. Each sign or symptom was graded on a scale of 0-3 (absent, mild, moderate or severe). For TSSS, three symptoms were assessed in the pityriasis versicolor studies: erythema, desquamation and pruritus. The criteria for Complete Cure were met if a subject had negative microscopy results and a TSSS of 0, making it more stringent than Effective Treatment.

In tinea pedis and tinea corporis/cruris, the criteria for Effective Treatment were met, if, at the same evaluation, a subject had negative microscopy, negative culture, sum of severity scores of erythema, desquamation and pruritus ≤ 2, individual severity scores for erythema, desquamation and pruritus ≤ 1 and individual severity scores for vesiculation, incrustation and pustules = 0. Complete Cure, with more stringent criteria than Effective Treatment, was defined as negative microscopy, negative culture, and TSSS for erythema, desquamation, pruritus, vesiculation, incrustation and pustule = 0.

a. Pityriasis versicolor

Table 2 presents the end of study Effective Treatment, Complete Cure and Negative Microscopy rates for the individual studies and the pooled intent-to-treat (ITT) population in the pityriasis versicolor studies. A total of 115 Lamisil and 72 placebo treated subjects were included in the pooled ITT population for this indication. Three Lamisil-treated subjects and no placebo-treated subjects were excluded from the pooled ITT population, the reason for exclusion was "no efficacy follow-up."

TABLE 2. Rates for Effective Treatment, Complete Cure and Negative Microscopy at end of study SFG 203 and SFG 302 (pityriasis versicolor)(ITT population)

Study	Effective Treatment			Complete Cure			Negative Microscopy		
	Lamisil % (n/N)	Placebo % (n/N)	P-Value CMH Test	Lamisil % (n/N)	Placebo % (n/N)	P-Value CMH Test	Lamisil % (n/N)	Placebo % (n/N)	P-Value CMH Test
SFG 203	75% (21/28)	14% (4/29)	< 0.001	71% (20/28)	14% (4/29)	< 0.001	75% (21/28)	14% (4/29)	< 0.001
SFG 302	73% (63/86)	10% (4/41)	<0.001	67% (58/86)	10% (4/41)	< 0.001	74% (64/86)	10% (4/41)	< 0.001
Pooled	74% (84/114)	11% (8/70)	ND	68% (78/114)	11% (8/70)	ND	75% (85/114)	11% (8/70)	N/D

Note: End of study is the last non-missing post-baseline observation.
CMH indicates the Cochran-Mantel-Haenszel test (adjusted for center) for treatment comparisons.
(n/N) = number of responders for variable/number of subjects evaluated for variable.
ND = not done

At End of Study, Lamisil was shown to be statistically significantly ($p \leq 0.001$) superior to placebo for all three of these measures of efficacy in both studies.

According to the sponsor, in the two studies, the mean TSSS at baseline ranged from (the maximum possible score was 9). In the pooled Lamisil group, the mean TSSS at the End of Study was 0.6 compared to 2.7 for the pooled placebo group. Effective Treatment required, in addition to negative microscopy, a TSSS ≤ 1. This TSSS represents a notable decrease in clinical severity from baseline, indicates minimal clinical manifestations of the infection, and thus provides a valuable and meaningful clinical indicator of a successful outcome not achieved by the placebo group.

The microscopy evaluation showed that Lamisil was significantly superior to placebo ($p < 0.001$) at End of Study for both studies.

The recurrence rate at the End of Study was 7%(8/84) for the Lamisil pooled group compared to

30%(6/20) in the placebo group.

For Effective Treatment, Complete Cure, and Negative Microscopy statistically significant differences in favor of Lamisil compared to placebo occurred by week 1 and continued through the End of Study evaluations, depending on the study. The response rates were progressive, thus the sponsor proposes that the patients should be informed that full therapeutic benefit may only be seen several weeks after end of treatment.

b. Tinea pedis and corporis/cruris

A total of 186 subjects were enrolled in two tinea pedis studies of whom 133 (82 Lamisil; 51 placebo) were included in the pooled ITT population. The most common reason for exclusion from the ITT population was delayed exclusion (negative baseline culture) which accounted for 51 subjects (27% in the pooled group). The data for two subjects, one in each treatment group, were excluded from the ITT population because of "no efficacy follow-up". In the tinea corporis/cruris study, 83 subjects were enrolled, of whom 62 (29 Lamisil, 33 placebo) were included in the pooled ITT population. The most common reason for exclusion from the ITT population was delayed exclusion , which accounted for 10 subjects in each treatment group; the data for one subject in the Lamisil treatment group was excluded because of "no efficacy follow-up".

Table 3 presents the End of Study Effective Treatment, Complete Cure and Negative Mycology rates for the individual studies and the pooled ITT population in the indications of tinea pedis and tinea corporis/cruris.

In the two tinea pedis studies, at End of Study, Lamisil was shown to be statistically significantly ($p \leq 0.001$) superior to placebo in all three of these measures of efficacy. The efficacy results observed at End of Study in the tinea corporis/cruris study ($p<0.001$) for Effective Treatment are consistent with the results shown in the two tinea pedis studies.

In the two tinea pedis studies, the mean TSSS at baseline ranged from 6.1 to 7.0 (the maximum possible score was 18). Most subjects had baseline TSSS of 5-7. At End of Study, in the two studies, the mean TSSS for the Lamisil 1% treatment group was significantly reduced ($p<0.05$) compared to the placebo group. The mean TSSS at baseline and End of Study in the tinea corporis/cruris study parallel those seen in the tinea pedis studies. The primary efficacy variable, required, in addition to Negative Mycology, a TSSS ≤ 2. According to the sponsor this TSSS represents a notable decrease in clinical severity from baseline, indicates minimal clinical manifestations of the infection, and thus provides a valuable and meaningful clinical indicator of successful outcome.

TABLE 3. End of Study rates for Effective Treatment, Complete Cure and Negative Mycology in tinea pedis and tinea corporis/cruris (ITT population).

Study	Effective Treatment				Complete Cure				Negative Mycology			
	LAM 1% 5 days % (n/N)	LAM 1% 1 wk % (n/N)	PBO % (n/N)	p-Value CMH Test	LAM 1% 5 days % (n/N)	LAM 1% 1 wk % (n/N)	PBO % (n/N)	p-Value CMH Test	LAM 1% 5 days % (n/N)	LAM 1% 1 wk % (n/N)	PBO % (n/N)	p-Value CMH Test
Tinea pedis												
SFG 102	86% (19/22)	–	15% (3/20)	<0.001	45% (10/22)	–	5% (1/20)	0.002	95% (21/22)	–	15% (3/20)	<0.001
SFG 202	–	64% (25/39)	26% (8/31)	0.001	–	38% (15/39)	16% (5/31)	0.019	–	82% (32/39)	32% (10/31)	<0.001
Pooled	86% (19/22)	64% (25/39)	22% (11/51)	ND	45% (10/22)	38% (15/39)	12% (6/51)	ND	95% (21/22)	82% (32/39)	25% (13/51)	ND
Tinea corporis/cruris												
SFG 201	–	83% (24/29)	21% (7/33)	<0.001	–	55% (16/29)	12% (4/33)	<0.001	–	90% (26/29)	39% (13/33)	<0.001

Note: End of Study is last non-missing post-baseline observation.
CMH indicates the Cochran-Mantel-Haenszel test (adjusted for center) for treatment comparisons
LAM = Lamisil Emulsion Gel
PBO = placebo (vehicle)
D = not done
- = not applicable
(n/N) = number of responders for variable/number of subjects evaluated for variable

Table 4 presents the response rates at End of Study by organism at baseline for the two tinea pedis studies.

TABLE 4. Response rates (%, n/N) at End of Study by organism at baseline (tinea pedis studies pooled) (ITT population)

Organism	Effective Treatment			Negative Mycology		
	LAM 5 days % (n/N)	LAM 1 wk % (n/N)	PBO % (n/N)	LAM 5 days % (n/N)	LAM 1 wk % (n/N)	PBO % (n/N)
Pooled: SFG 202 and SFG 102						
T. rubrum	86% (12/14)	60% (18/30)	18% (7/40)	93% (13/14)	80% (24/30)	20% (8/40)
T. mentagrophytes	86% (6/7)	71% (5/7)	44% (4/9)	100% (7/7)	86% (6/7)	56% (5/9)
E. floccosum	100% (1/1)	100% (2/2)	0% 0/1	100% (1/1)	100% (2/2)	0% (0/1)

Note: Of the 133 ITT patients, only 111 patients are included in this table; Lamisil 1% (61 patients) and placebo (50 patients). Patients from the 3% Lamisil group (21 patients) are not included and one patient from the placebo group is not included (organism isolated at baseline was not specified).
Note: End of Study is last non-missing post-baseline observation. LAM = Lamisil Emulsion Gel, PBO = placebo (vehicle)
(n/N) = number of responders for variable/number of subjects evaluated for variable

Trichophyton rubrum, Trichophyton mentagrophytes and *Epidermophyton floccosum* accounted for all but one of the infections observed at baseline in the tinea pedis studies. The majority of isolates were *Trichophyton rubrum* (84/111). Although the number of organisms isolated at baseline was small for *Trichophyton mentagrophytes* (23/111) and *Epidermophyton floccosum* (4/111), all three organisms responded well to Lamisil treatment (Table 4). Lamisil Effective Treatment rates at End of Study by organism at baseline were: *Trichophyton rubrum* 68% (30/44), *Trichophyton mentagrophytes* 79% (11/14) and *Epidermophyton floccosum* 100% (3/3). The eradication rates by organism for these studies were: *Trichophyton rubrum* 84% (37/44), *Trichophyton mentagrophytes* 93% (13/14) and *Epidermophyton floccosum* 100% (3/3).

Table 5 presents the response rates at End of Study by organism at baseline for the tinea corporis/cruris study.

TABLE 5. Response rates (%, n/N) at End of Study by organism at baseline (tinea corporis/cruris study SFG 201) (ITT population)

	Effective Treatment		Negative Mycology	
Organism	**LAM 1% 1 wk % (n/N)**	**PBO % (n/N)**	**LAM 1% 1 wk % (n/N)**	**PBO % (n/N)**
T. rubrum	81% (22/27)	14% (4/29)	81% (22/27)	21% (6/29)
T. mentagrophytes	100% (1/1)	NA	100% (1/1)	NA
E. floccosum	100% (1/1)	100% (2/2)	100% (1/1)	100% (2/2)
M. canis	NA	0% (0/1)	NA	0% (0/1)
T. violaceum	NA	100% (1/1)	NA	100% (1/1)

Note: End of Study is last non-missing post-baseline observation.
LAM = Lamisil Emulsion Gel, PBO = placebo (vehicle)
(n/N) = number of responders for variable/number of subjects evaluated for variable
NA = not applicable; no patient with this organism

In the tinea corporis/cruris studies, the organisms were present in proportions which were similar to the tinea pedis studies at baseline, the majority being *Trichophyton rubrum* (56/62). Lamisil Effective Treatment at End of Study for *Trichophyton rubrum* was 81% (22/27) versus 14% (4/26) with placebo, which concur with the tinea pedis results. Again, the number of subjects who presented with *Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis* and *Trichophyton. violaceum* in the tinea corporis/cruris study was small.

The sponsor states that the clinical response rates for Lamisil-treated subjects with tinea pedis and

corporis/cruris was progressive during post-treatment follow-up, so subjects should be informed that full clinical benefit may only be achieved several weeks after completion of therapy.

2. *IN VITRO* STUDIES

The sponsor has not submitted any new *in vitro* data under this application. Reference is made to NDA 20-192, Lamisil 1% Cream, approved December 30, 1992, and NDA 20-539, Lamisil Tablets, approved May 10, 1996. The microbiology portion of NDA 20-192 was reviewed by Dr. Soprey on December 31, 1991, April 27, and November 13, 1992. The microbiology portion of NDA 20-539 was reviewed by Dr. Creedon on July 21, 1995. Dr. Soprey's review resulted in the following list of organisms for the *in vivo* and *in vitro* lists in the approved Product Insert (PI) of Lamisil 1% cream for treatment of interdigital tinea pedis, tinea cruris and tinea corporis:

In vivo (clinical efficacy) list:
Epidermophyton floccosum
Trichophyton mentagrophytes
Trichophyton rubrum

In vitro inhibition list:
Microsporum canis
Microsporum gypseum
Microsporum nanum
Trichophyton verrucosum

Dr. Creedon's review resulted in the following list of organisms for the *in vivo* and *in vitro* lists in the approved Product Insert (PI) of Lamisil 250 mg tablets for treatment of onychomycosis:

In vivo(clinical efficacy) list:
Trichophyton mentagrophytes
Trichophyton rubrum

In vitro inhibition list:
Epidermophyton floccosum
Microsporum gypseum
Microsporum nanum
Trichophyton verrucosum
Candida albicans
Scopulariopsis brevicaulis

3. ORGANISMS ALLOWED IN THE LABEL

It is the current policy of this Division (DAIDP, HFD-520) to include in the *in vitro* section of a drug product's label, only those organisms which are pathogens in the clinical indications being approved. In addition there must be *in vitro* data available on at least 100 resent clinical isolates tested in more than one laboratory. The MIC_{90} for these isolates must be reasonably low.. Consequently, only those organisms involved in pityriasis versicolor, tinea pedis, tinea cruris, and tinea corporis may potentially be placed in the *in vitro* microbiology section of the package insert for the 1% Emulsion Gel formulation. Table 6 summarizes the causative agents of tinea pedis, corporis and cruris.

TABLE 6. Causative agents of tinea pedis, corporis, cruris, barbae, capitis, faciei, manum, and unguium in humans.

Organism	Tinea Barbae	Tinea Capitis	Tinea Corporis	Tinea Cruris	Tinea Faciei	Tinea Manum	Tinea Pedis	Tinea unguium/ Onychomycosis
Dermatophytid molds								
Trichophyton rubrum	X	X[a]	X	X	X	X	X	X
Trichophyton tonsurans		X	X			X	X	X
Trichophyton mentagrophytes	X	X	X	X		X	X	X
Trichophyton violaceum	X	X	X			X		X
Trichophyton verrucosum	X	X	X	X	X		X	X
Trichophyton schoenleinii		X	X					X
Trichophyton concentricum			X		X			
Epidermophyton floccosum			X	X			X	X
Microsporum canis	X	X	X		X			X
Microsporum audouinii		X	X					
Microsporum gypseum	X	X	X		X			
Microsporum nanum		X[a]	X[a]					
Microsporum distortum		X						
Microsporum ferrugineum		X						

Organism	Tinea Barbae	Tinea Capitis	Tinea Corporis	Tinea Cruris	Tinea Faciei	Tinea Manum	Tinea Pedis	Tinea unguium/ Onychomycosis
Nondermatophytid molds								
Scopulariopsis brevicaulis								X
Scytalidium spp.								X
Acremonium spp.								X
Fusarium spp.								X
Hendersonula spp.								X
Yeast								
Candida albicans								X
Candida parapsilosis								X[a]
Candida krusei								X[a]
Candida tropicalis								X[a]

[a] It is rarely the causative agent of the indicated dermatophytosis.

It is evident from table 5 and the pivotal studies summarized above, that dermatophytes are the most common cause of the tineas for which the sponsor is seeking approval.

Table 7 summarizes the *in vitro* activity of terbinafine hydrochloride and was constructed by Dr. Creedon from the data submitted by the sponsor under NDAs 20-192 and 20-539. These data shows that terbinafine hydrochloride has good activity against the dermatophytes but a limited activity against *Fusarium* and *Candida* spp. In fact the sponsor states in NDA 20-192, page 07-00011 of Vol. 47, that "Against *C. albicans* the MIC of SF 82-327 (terbinafine hydrochloride) was fungistatic; fungicidal effects were observed only at concentrations 5 times the MIC."

TABLE 7. ***In vitro*** **susceptibility profile of terbinafine hydrochloride.**

Microorganism	**No. of Isolates**	**MIC range (μg/mL)**	**MIC_{90} range (μg/mL)**
Trichophyton rubrum	66		
Trichophyton mentagrophytes	86		
Trichophyton tonsurans	11		
Epidermophyton floccosum	26		
Microsporum canis	54		
Microsporum gypseum	13		
Microsporum nanum	8		
Aspergillus flavus	32		
Aspergillus fumigatus	102		
Aspergillus nidulans	3		
Aspergillus niger	56		
Aspergillus terreus	17		
Scopulariopsis brevicaulis	101		
Fusarium spp.	27		
Candida albicans	268		
Candida glabrata	45		
Candida krusei	18		
Candida parapsilosis	73		
Candida pseudotropicalis	7		
Candida tropicalis	36		

The sponsor have requested that the following organisms be placed in the *in vitro* section of the package insert:

Microbiologist's comments: Each organism will be discussed separately bellow.

Microbiologist's comments: The list should be written in an alphabetical order. If any of these organisms are not granted by the reviewing medical officer then they will be omitted from this list.

4. PACKAGE INSERT

The **Microbiology** subsection of the package insert should be rewritten as follows:

Microbiology

CONCLUSION & RECOMMENDATIONS:

The application is approvable form the clinical microbiology viewpoint under section 505 (b) of the Act. The sponsor should be notified to revise the Microbiology subsection of the package insert as indicated on page 13 of this review.

/S/

Sousan S. Altaie, Ph. D.
Clinical Microbiology Review Officer

cc: Orig. NDA 20-749
HFD-540/Division File
HFD-520/Micro/S Altaie
HFD-540/MO/E Toombs
HFD-540/Pharm/K Mainigi
HFD-540/Chem/J Vidra
HFD-540/Stat/S Thomson
HFD-160/Micro/N Sweeney
HFD-540/ Biopharm/D Bashaw
HFD-540/CSO/S. Kummerer

Concurrence Only:
HFD-540/Dir/J Wilkin
HFD-520/SMicro/A Sheldon
1/30/98
2/3/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-846

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JAN 7 1998

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-846 SUBMISSION DATE: 4/29/97

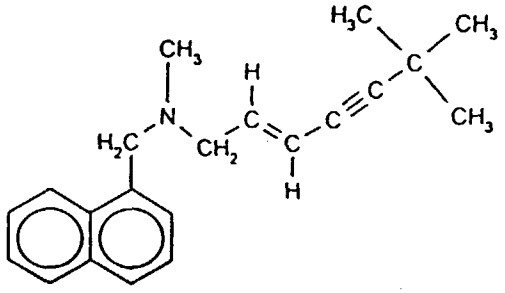
PRODUCT: Lamisil® DermGel™
Terbinafine 1% Topical Emulsion Gel

SPONSOR: Novartis
Pharmaceutical Corp. REVIEWER: Veneeta Tandon, Ph.D.

Review of a NDA

I. Background

Terbinafine is a synthetic allylamine antifungal compound which has been shown to exert its antifungal effect by inhibiting squalene epoxidase, a key enzyme in ergosterol biosynthesis. This action leads to a deficiency of ergosterol and to corresponding accumulation of squalene within the fungal cell. Lamisil® DermGel™ is indicated for the topical treatment of the following dermatological infections: pityriasis versicolor due to *Malassezia furfur*, and tinea pedis (athlete's foot), tinea cruris (jock itch) or tinea corporis (ringworm) due to *Trichophyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum.*



Chemically, terbinafine is (E)-N-(6,6-Dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine and is highly lipid soluble which is thought to account for the preferential uptake into the skin.

Lamisil® DermGel™ is the third topical formulation of Lamisil® that has been developed by Novartis. Lamisil® Cream 1% was approved on December 30, 1992 (NDA 20-192) for the treatment of tinea pedis and tinea corporis/cruris. An NDA for Lamisil® Solution 1% for the treatment of tinea pedis, tinea corporis/cruris and pityriasis versicolor (NDA 20-749) was approved on October 17, 1997. In addition Lamisil® Tablets was approved on May 10, 1996 (NDA 20-539).

Lamisil® DermGel™ has been formulated to provide the physician with an additional formulation treatment option and has the reported advantage in treating large surface areas of the body, as well as hairy areas in the body where cream would be inconvenient, messy or otherwise unacceptable.

II. Recommendation

The plasma concentrations of terbinafine after once daily topical application of 1% Lamisil® DermGel™ was about 37 times lower than that observed after once a day oral administration of 250 mg terbinafine in patients. The absolute bioavailability was estimated to be < 5%. In normal volunteers, the plasma concentrations were about 45 times lower after topical application of the Gel as compared to the oral administration. A comparative study of the dermatopharmacokinetics of the Gel vs . the Cream dosage form indicates that the Gel penetrates the stratum corneum as well as the cream. After 5 days of the treatment, the AUC after the Gel application was significantly higher than that of the Cream ($p<0.001$) and the C_{max} was also greater for the Gel ($0.001 \leq p<0.01$), however, no significant difference in absorption was observed after 7 days of application of the Gel and the cream. The $t_{1/2}$ was 27.2 hours after the application of the gel and 35.2 hours after that of the cream.

The sponsor has adequately investigated the in-vivo pharmacokinetics of terbinafine and has compared the dermal penetration to that of the 1% cream dosage form. From the pharmacokinetic standpoint the sponsor has demonstrated that the systemic absorption is increased in the diseased skin, but is markedly inferior to that of the oral tablet. The pharmacokinetic information provided is satisfactory and the application is approvable, provided the labeling issues are resolved.

INDEX

SFW 410-E-00*	*	*	*	*	*	*	*	*	20
SFG 205-E-00*	*	*	*	*	*	*	*	*	25
SFG 101-E-00*	*	*	*	*	*	*	*	*	31

III. Formulation

The to be marketed formulation is as follows:

Components	Amounts for 100 gm of drug product
Terbinafine Base, Sandoz	1.0 g
Butylated hydroxytoluene, NF	g
Sodium Hydroxide, Ph.Eur	g
Benzyl Alcohol, NF	g
Sorbitan Monolaurate, NF	g
Carbomer 974P, NF	g
Polysorbate 20, NF	g
Isopropyl Myristate, NF	g
ethanol	g
Water purified, USP	8

IV. Analytical Methods

V. Summary of In-Vivo Pharmacokinetic Trials

Study No. SFW 409-E-00

Determination of plasma concentration of terbinafine after repeated applications as a Lamisil® 1% Emulsion gel to the normal skin in healthy volunteers.

A total of 12 normal Caucasians subjects (6M/6F) completed the trial. The study medication was applied once daily for seven consecutive days onto a skin surface area representing 20% of the body surface area. The surface of application in this study is 25

times that used the study with 1% cream and 1% solution. mg of emulsion gel containing mg of terbinafine was applied per cm^2 of the skin. Body surface area was calculated using Dubois and Dubois equation: $BSA(m^2)= 0.007184 \times Height\ (cm)^{0.725} \times Weight\ (kg)^{0.425}$. Total amount of gel applied daily in grams was 4 x BSA (m^2). Subjects received a mean daily application of 67.5 ± 5.5 mg of terbinafine. The subjects were asked to wash their body surface with soap and water one hour prior to each application. The treated area was not to be covered till one hour after the application.
Plasma concentration of terbinafine were quatifiable from 2-4 hours post application for 4 subjects and from 10 hours onwards for all subjects. The individual plasma concentrations along with study summary is attached in Appendix I (pages 15-19). Due to very low plasma levels, only the concentrations measured on Day 7 were used for the pharmacokinetic evaluation.

The pharmacokinetic parameters of terbinafine at Day 7 are summarized in the table below:

Parameter	Mean	SD	Range
T_{max} (h)	7.33	3.45	
C_{max} (ng/ml)	3.82	2.05	
AUC_{0-24} (h.ng/ml)	62.55	46.54	

With regard to the mean AUC of 2306.7 h.ng/ml after intravenous administration of 80 mg of terbinafine in healthy volunteers, the absolute bioavailability can be estimated to < 5% (Data from a "Single rising intravenous dose tolerability study of Lamisil in healthy male subjects *Document* 303-617). The plasma concentrations of terbinafine, after repeated once daily application of 55-77 mg topical terbinafine were about 45 times lower than those observed after repeated once a day oral administration of 250 mg terbinafine. The AUC is < 1% of that seen following repeated oral administration of the marketed 250 mg tablet to healthy volunteers for 28 days (terbinafine mean AUC of 10,481 ng.h/ml)

Pharmacokinetics of metabolite

The individual plasma concentrations of the metabolite of terbinafine is attached in Appendix I (page 18). At Day 1 all the plasma concentrations were below the LOQ except for one subject. At day 7, 6/12 subjects had a few quantifiable concentrations. No pharmacokinetic assessment was possible on these data.

Comment

- This study is adequately designed and all relevant information in has been provided.
- Due to a low number of subjects in this study, a meaningful gender analysis was not possible, although, the data did not show any trend in the males or females.

Study No. SFW 410-E-00

Determination of plasma concentration of terbinafine after repeated applications as a Lamisil® 1% Emulsion gel to the diseased skin inpatients with Tinea cruris/Corporis.

This study was also carried out in 12 patients (6M/6F). Terbinafine was applied once a day for 7 consecutive days as 1% Lamisil® Emulsion gel on diseased area(s) of skin as well as 2.5 cm wide margin of healthy skin around the lesion(s). The inclusion criteria for the patients was that the total area of the diseased skin should have a surface of 20-500 cm^2 and must not be oozing. The mean daily amount of terbinafine applied ranged from 20.4 to 92.1 mg. The amount of gel applied was determined by weighing the tube and gloves before and after the application procedure. The evening before the first application patients body was thoroughly washed using soap and water. The treated site was again washed prior to the next application. The application site was allowed to dry for 15 minutes after which the patient was allowed to dress.

Due to very low concentrations of the drug and metabolite on Day 1, only the concentrations measured on Day 7 were used in the pharmacokinetic evaluation. Individual plasma concentrations are shown in Appendix I (page 22). The noncompartmental pharmacokinetic parameters of terbinafine at Day 7 are summarized in the table below, the inconsistent nature of the plasma concentration data did not allow for calculation of $t_{1/2}$:

Parameter	Mean	SD	Range
T_{max} (h)	7.83	7.11	
C_{max} (ng/ml)	2.48	1.85	
AUC_{0-24} (h.ng/ml)	40.54	36.30	
AUC_{0-24} weighted (h.ng/ml)*	41.51	27.68	

*weighted by the actual individual dose applied on Day 7

With regard to the mean AUC of 2306.7 h.ng/ml after intravenous administration of 80 mg of terbinafine in healthy volunteers, the absolute bioavailability can be estimated to <5%. The plasma concentrations of terbinafine, after repeated once daily application of 21-92 mg topical terbinafine were about 37 times lower than those observed after repeated once a day oral administration of 250 mg terbinafine.

Pharmacokinetics of metabolite

The individual plasma concentrations of the metabolite of terbinafine is attached in Appendix I (page 23). At Day 1 all the plasma concentrations were below the LOQ. At day 7, 2/12 subjects had a few quantifiable concentrations. No pharmacokinetic assessment was possible on these data.

Comments

- Normalizing the data for normal volunteers and patients for similar body surface area coverage, it appears that the Cmax and AUC were approximately 24 fold higher in the

patients. However, since Lamisil® Oral tablets are available, which produce even higher levels, this is not of any clinical importance.

- A discrepancy between the study conducted in normal volunteers and the patients is that the normal volunteers were not allowed to wear clothes till 1 hour after the application of the test medication, whereas the patients were allowed to cover the area after 15 minutes of the application of the test medication. This adds up to the difficulty in comparing the results from the study conducted in normal volunteers versus patients.

Study # SFG 205-E-00

A study to investigate the skin pharmacokinetics of Lamisil® 1% emulsion gel compared to Lamisil® 1% cream in healthy subjects, following a single application on one, five or seven consecutive days.

This study was designed to determine whether increasing the number of applications of 1% emulsion gel and 1% cream increases the concentrations of terbinafine in the stratum corneum, whether single applications for 1, 5 or 7 consecutive days results in levels of terbinafine being detected for longer periods at higher concentrations for the same period in the skin and following cessation of treatment and, whether there are differences in tissue levels or duration between the Gel and the Cream. 36 healthy Caucasian volunteers (3 M/ 3F per treatment regimen) completed this study. 0.5 gm of either the gel or the cream were applied on each visit to two areas on the back each measuring 5x3 inches. Skin biopsies were taken at intervals. Results are shown in detail in Appendix I (pages 25-30).

In this study the skin concentration has been calculated twice, once with a LOQ of 0.18 ng/cm^2 and then by raising the LOQ to 2 ng/cm^2. The later approach was considered more acceptable based on ± 15% CV for the 2 ng/ cm^2 standard. This change in the LOQ greatly affected the $t_{1/2}$ values. The % decrease in $t_{1/2}$ ranged from % (1% cream, day 7) to % (1% Emulsion gel, day 5).

For each 2.5 micron thick skin biopsy, the total stratum corneum concentration was calculated by adding the terbinafine concentrations across the five stratum corneum levels. If any of the five level concentrations were missing (e.g. due to contamination), the total stratum corneum concentration was set to missing. The results show that penetration occurs down to level 5, with the highest concentration found in level 1 and 2. Results show that the mean terbinafine concentrations in total stratum corneum were still detectable after stopping 1 day of treatment with Lamisil® Gel and Cream, and up to 168 hours (7 days) in all subjects in the 5-day and 7-day Lamisil® Gel group and 7-day Cream group. Terbinafine levels were only detectable for up to 96 hours after stopping the 5 days treatment with the Cream.

The pharmacokinetic parameters were, the AUC over 7 days after the last application, the C_{max} over the 7 days after the last application, the T_{max} after the last application, the elimination rate constant and the $t_{1/2}$ measured from the last application. The results are summarized in the Table below. The asterix (*) AUC, C_{max} and $t_{1/2}$ values

are obtained with the LOQ of < 0.18 ng/cm2 and have been provided in the table below for comparison purposes.

Mean Total Stratum Corneum Pharmacokinetic Parameters						
	Lamisil Gel			Lamisil Cream		
	1 day	5 days	7 days	1 day	5 days	7 days
No. of subjects	6	6	6	6	6	6
AUC $_{0-t}$ (ng.hr/cm^2)(sd)	8238(962)	9821(594)	12279(619)	7214(960)	8180(280)	11478(221)
*AUC $_{0-t}$ (ng.hr/cm^2)(sd)	8295(956)	10287(551)	12650(626)	7271(951)	8480(268)	11754(256)
C_{max} (ng/cm^2) (sd)	638 (54.1)	891(93.5)	908.8(91)	717.7(76.7)	746(54.1)	944(105.9)
*C_{max} (ng/cm^2) (sd)	638 (54.1)	891(93.5)	908.8(91)	717.7(76.7)	746(54.1)	944(105.9)
$t_{1/2}$ (hours) (sd)	n/a	17.2(3.0)	27.2(5.1)	n/a	14.4(2.4)	35.2(9.2)
*$t_{1/2}$ (hours) (sd)		36.5 (5.5)	47.2(3.0)		21.3(1.5)	44.1(3.4)

T_{max} is not presented due to lack of variability-it was always 4 hours
n/a= not applicable due to insufficient data,
LOQ of terbinafine concentrations <2.0 ng/cm^2, * <0.18 ng/cm^2

Statistical comparisons were done on logarithmically transformed AUC and Cmax. Results are summarized in the Table below,

Comparisions of Pharmacokinetic Parameters				
		AUC 0-t	Cmax	t1/2
Lamisil® Gel vs. Cream	1 day	**	n.s.	n/a
	5 days	***	**	n.s.
	7 days	n.s.	n.s.	*
Lamisil® Gel	1 day vs. 5 days	***	***	n/a
	1 day vs. 7 days	***	***	n/a
	5 days vs. 7 days	***	n.s.	**
Lamisil® Cream	1 day vs. 5 days	*	n.s.	n/a
	1 day vs. 7 days	***	***	n/a
	5 days vs. 7 days	***	***	***

***p<0.001,**0.001≤p<0.01, *0.01≤p<0.05, (*) 0.05≤p<0.1, n.s. = not significant
n/a= not applicable due to insufficient data,
LOQ for terbinafine concentrations < 2.0 ng/cm^2

For AUC and C_{max}, estimates of the pairwise geometric mean ratios were calculated, together with 95% confidence intervals for the ratios. For $t_{1/2}$, estimates of the pairwise mean differences were calculated, together with 95% confidence intervals for the mean differences.

The results indicate that increasing the number of applications of Gel and Cream increases the concentration of terbinafine in the stratum corneum as well as the duration at which detectable concentrations of terbinafine are found. A greater AUC_{0-t} and C_{max}

values for terbinafine in the total stratum corneum were reached after 1 and 5 days of treatment with Lamisil 1% Emulsion Gel compared to 1% Lamisil cream. The elimination half life was significantly longer for the Gel after 5 days treatment as compared to the Cream.

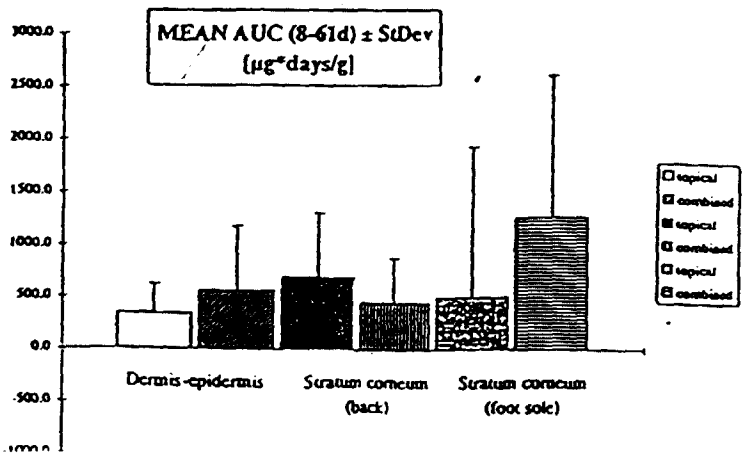
Study # SFG 101-E-00

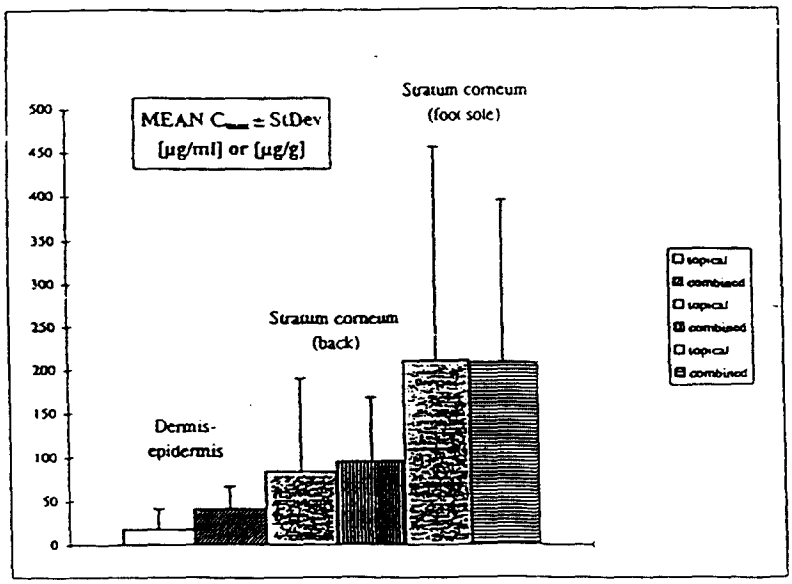
Randomized double-blind parallel-group study on healthy male subjects, with emulsion gel topically applied for 1 week in combination with either 1-week orally administered Lamisil or placebo.

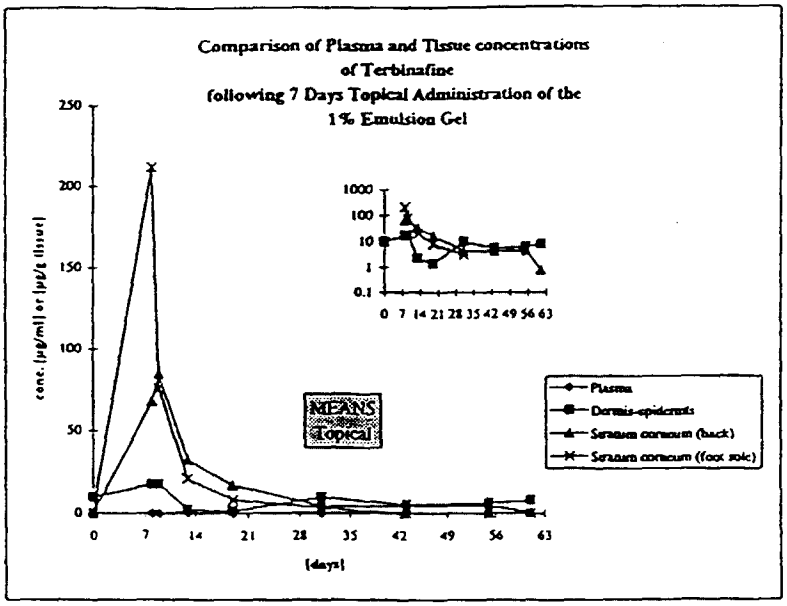
This study was designed to investigate whether topically applied Lamisil 1% Derm Gel, co-administered with terbinafine 250 mg/day orally (both for 1 week) results in higher tissue levels of terbinafine than topically applied Derm Gel alone. 24 healthy Caucasian males (12 per treatment regimen) completed this study. Details of the study design is given in the Appendix on pages 31-39. The treatment duration was 7 days, followed by 54 days post treatment period during which the skin and plasma pharmacokinetics were investigated. Lamisil Emulsion Gel was to be applied to the soles of the subjects feet and to the whole of their back once daily and tablet was to be taken once daily in the morning. Pharmacokinetic variables were derived from terbinafine levels measured in the tissue (foot-sole, back) and plasma samples taken. AUC was calculated individually for the period between Day 8 and 61.
The results are summarized in the table below. Details are provided in the Appendix 1 (pages 31-39)

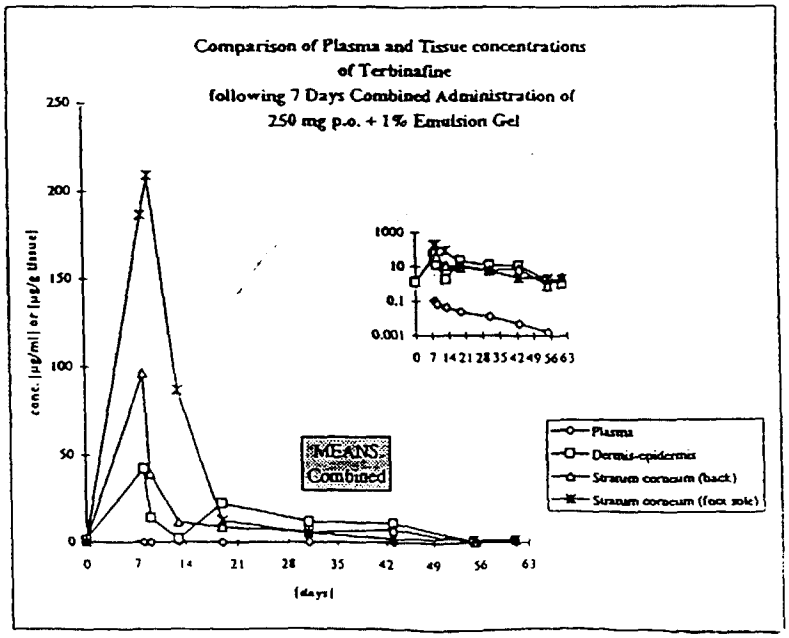
Tissue	Treatment	AUC(8-61d) ± SD µg.days/g	Cmax ± SD µg/mL	Tmax days
Plasma	Topical	0	0	0
Plasma	Combined	0.9 ± 0.6	0.106 ± 0.056	8
Dermis-epidermis	Topical	336.8 ± 553.1	17.6 ± 24.0	9
Dermis-epidermis	Combined	559.8 ± 585.1	42.2 ± 25.1	8
Stratum- (back)	Topical	703.1 ± 412.0	84.6 ± 107	9
Stratum- (back)	Combined	457.0 ± 318.0	96.4 ± 74	8
Stratum-(foot sole)	Topical	507.8 ± 494.6	2117.7 ± 244.1	8
Stratum-(foot sole)	Combined	1277.8 ± 1060.7	209.2 ± 186.2	9

The mean AUC and C_{max} in the different tissues is shown in the bar and line diagram below.




MEAN C = StDev
[µg/ml] or [µg/g]
Stratum corneum
(foot sole)
Stratum corneum
(back)
Dermis-
epidermis
500
450
400
350
300
250
200
150
100
50
0
topical
combined
topical
combined
topical
combined


Comparison of Plasma and Tissue concentrations
of Terbinafine
following 7 Days Topical Administration of the
1% Emulsion Gel
conc. [µg/ml] or [µg/g tissue]
[days]
MEANS
Topical
Plasma
Dermis-epidermis
Stratum corneum (back)
Stratum corneum (foot sole)


Comparison of Plasma and Tissue concentrations
of Terbinafine
following 7 Days Combined Administration of
250 mg p.o. + 1% Emulsion Gel
conc. [µg/ml] or [µg/g tissue]
[days]
MEANS
Combined
Plasma
Dermis-epidermis
Stratum corneum (back)
Stratum corneum (foot sole)

No terbinafine was measurable in *plasma samples* from subjects who were treated topically with oral placebo co-adminsitration. I believe this is due to the higher LOQ in plasma for this study as compared to the others (9.3 ng/ml vs 1 ng/ml in the other studies) Subjects who received once a day 250 mg orally + topical treatment with 1% gel were all systemically exposed to terbinafine. Highest levels were 1 day after the stop of medication (Day 8). In none of the samples from day 61 was terbinafine measurable. The individual concentrations with figures are shown in the Appendix on pages 32-33.

The highest mean concentration from the *stratum corneum from the back* was measured on day 8 for the combined treatment and day 9 for the topical treatment. The mean peak concentrations were 84.6 ± 107 and 96.4 ± 74 μg/g for the topical and combined, respectively. The inter-individual variability (CV%) was high between 65 and 293%. 11 out of 24 subjects had detectable levels of terbinafine on day 61, 10 of these were on combined treatment. The individual concentrations are shown on page 34 of the Appendix.

When compared to stratum corneum from the back, terbinafine appeared to be about 2 times higher concentrated in *stratum corneum from the foot soles*. The mean peak levels of 211.7 ± 244.1 and 209.2 ± 186.2 μg/g were found 1 and 2 days after the cessation of drug application for the topical and combined, respectively. The inter-individual variability (CV%) was high between 65 and 346%. The variabilities are shown graphically in the figure above.

The terbinafine measurements in *dermis-epidermis* were impaired by the blank back ground observed in all samples at study baseline (day 0). Overall mean of this blank interference (15 μg/g) was substracted from all individual concentrations. The inter-individual variability (CV%) was high between %. Due to the back ground interference this data does not carry much significance.

Terbinafine levels appear to be higher in the combined treatment, with the exception in the case of stratum corneum from the back. Due to the high inter-subject variability it is difficult to obtain the statistical significance of these findings. The mean peak concentrations (C_{max}) in each tissue is similar when comparing the topical with the combined application. This suggests that the topical application of the gel contributes mainly to the levels of drug found in the skin. An apparent difference could only be found in the mean AUC, being higher with combined treatment with the exception of the stratum corneum from the back, suggesting that the combined treatment extends the time for the maintenance of fungicidal concentrations in the skin.

Comments

- Due to high inter-subject variability and use of subjects with normal skin, it is difficult to draw any significance from this study. No labeling claims have been made from this study.

VI. Conclusions

Terbinafine is currently available as an 250 mg oral tablet and as 1% cream. A 1% spray dosage form has also been very recently approved. The sponsor has adequately demonstrated in-vivo pharmacokinetics of the 1% emulsion gel dosage form and compared it to that of the cream formulation. No additional pharmacokinetic information is required for approval. However, some labeling suggestions have been outlined below.

VII. Labeling Comments

Metabolism

It is unknown whether or not there is significant skin metabolism of topically applied terbinafine. Radiolabeled studies with oral dosage forms indicate that terbinafine is highly metabolized into a number of inactive metabolites which undergo conjugation and excretion into the urine. The primary metabolite seen in the urine (10% of the oral dose) is N-demethyl terbinafine. After topical application of Lamisil® DermGel™, 2/12 patients and 6/12 healthy volunteers had detectable levels of the N-demethyl metabolite in the plasma at day 7, with maximum concentration being 0.99 ng/mL and 2.57 ng/mL, respectively.

Elimination

Based on series of studies, the total stratum corneum half life of terbinafine when absorbed through the skin is ~14-35 hours, depending on the topical dosage form of terbinafine. In a study comparing the Lamisil® DermGel™ with the Lamisil Cream 1% dosage form, the total stratum corneum $t_{1/2}$ for terbinafine after Day 7 application of Lamisil® DermGel™ was 27.2 h vs. 35.2 h for Lamisil Cream 1% ($p < 0.05$). Approximately 75% of cutaneously absorbed terbinafine is eliminated in the urine, predominately as metabolites.

- For consistency the "Nursing Mothers" section should be identical to that recently proposed for Lamisil® Spray 1%.

/S/ 1/7/98

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. Edb 1/7/98

NDA
CC: [redacted] 20-846 (orig)
HFD-540/Div File
HFD-540/CSO/Kummer
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

AE

APPENDIX I

NDA/IND#: 20-846 Volume 1.8

Study Type: Bioavailability *Study* # SFW 409-E-00

Study Title: Determination of plasma concentration after repeated application to normal skin.

Study Site	
Clinical Site	*Analytical Site*

Study Design								
Single Dose	*Multiple Dose*	*Washout Period*	*Cross - over*	*Parallel*	*Other Design*	*Fasted/ Fed*	*FDA Diet*	*No. of fasted hrs.*
	X				Open, not controlled			

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X					

Subject Type			
Males		*Females*	
Age	*Weight*	*Age*	*Weight*
(Av 26)	kg (Av 63.8)	(Av 26)	kg (Av 63.8)

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
	12	6	6

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
All	once daily-7 dys	Emulsion Gel	1%	Z050 1294
	(67.5 mg/d)			

Sampling Times

Plasma (8 ml) **Day 1→ 0, 2, 4 10 & 24 hrs, Day 4→ 0 hrs, Day 7→ 0, 2, 4, 6, 10, 14, 24 & 48 hrs**

Assay Method: *Assay Sensitivity:* 1ng/ml Terbinafine, 0. 5ng/ml SDZ86621

Assay Accuracy:[Nominal / measured / % accuracy]; [1 / 0.95 / -5.1]; [5 / 4.99 / -0.1]; [200 / 191/ -4.4] for terbinafine.

[1 / 0.89 / -11]; [5 / 4.74 / -5.3]; [200 / 181.87 /-.91] for SDZ 86-621.

Labeling Claims from this Study: On Day 1, terbinafine was found in the plasma of eleven out of twelve subjects at 10 hours (mean of 2.2±1.36 ng/mL, limit of quantification-1 ng/mL). On Day 7 all subjects has quantifiable terbinafine levels. The highest measured plasma terbinafine concentration was ng/mL. The AUC_{0-24} on Day 7 was 62.6 ng.h/mL. This is 0.6% of the AUC_{0-24} in healthy subjects following 250 mg PO for 28 days (10,481 ng.h/mL).

BODY SURFACE AREA AND WEIGHT OF LAMISIL GEL (g) IN HEALTHY MALE AND FEMALE VOLUNTEERS

Subject number	Body surface area (m^2)	Amount of Gel to apply (g)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Mean
										5.72
										6.37
										6.64
										6.70
										6.74
										6.03
										7.51
										6.85
										7.71
										7.03
										6.79
										6.96
N	12	12	12	12	12	12	12	12	12	12
MEDIAN	1.744	6.976	6.78	6.84	6.69	6.79	6.795	6.815	6.835	6.77
MEAN	1.736	6.946	6.74	6.80	6.69	6.72	6.73	6.80	6.79	6.75
STD	0.143	0.573	0.57	0.58	0.57	0.56	0.55	0.56	0.54	0.55
STDERR	0.041	0.165	0.17	0.17	0.16	0.16	0.16	0.16	0.16	0.16
MIN										5.72
MAX										7.71
L.95% CL.	1.655	6.621	6.414	6.476	6.366	6.409	6.425	6.481	6.490	6.441
U.95% CL.	1.817	7.270	7.063	7.128	7.011	7.040	7.043	7.113	7.098	7.067

INDIVIDUAL PHARMACOKINETIC PARAMETERS OF TERBINAFINE (SF 86-327) AT DAY 7
after topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the nornal skin in 12 healthy volunteers

Subject Nr	Cmax [ng/ml]	tmax [h]	AUC[0-24h] [h.ng/ml]
N	12	12	12
MEAN	3.82	7.33	62.55
SD	2.05	3.45	46.54
SEM	0.59	0.99	13.43
CV [%]	53.76	47.00	74.41
MEDIAN	3.39	6.00	55.18
MINIMUM			
MAXIMUM			

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF TERBINAFINE (SF 86-327)
after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the normal skin in 12 healthy volunteers
(Values below the limit of quantification (1 ng/ml) were set to zero)

Subject Nr/Time(h)	Mean Daily Dose [mg] terbinafine	0.00	2.00	4.00	10.00	24.00	72.00
		Day 1					Day 4
N	12	12	12	12	12	12	12
MEAN	67.54	0.00	0.32	0.33	2.22	1.28	1.03
SD	5.54	0.00	0.59	0.78	1.36	0.91	1.18
SEM	1.60	0.00	0.17	0.22	0.39	0.26	0.34
CV [%]	8.20	N.C.	184.92	234.07	61.10	71.17	114.12
MEDIAN	67.65	0.00	0.00	0.00	1.69	1.48	0.70
MINIMUM							
MAXIMUM							

N.C.: not calculated

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF TERBINAFINE (SF 86-327)
after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the normal skin in 12 healthy volunteers
(Values below the limit of quantification (1 ng/ml) were set to zero)

Subject Nr/Time(h)	144.00	146.00	148.00	150.00	154.00	158.00	168.00	192.00	312.00
	Day 7								Day 14
N	12	12	12	12	12	12	12	12	11
MEAN	1.57	1.98	2.71	3.54	3.21	2.74	1.79	0.72	0.21
SD	1.61	1.95	2.60	2.10	2.15	2.27	1.39	0.91	0.47
SEM	0.47	0.56	0.75	0.61	0.62	0.65	0.40	0.26	0.14
CV [%]	103.02	98.43	95.98	59.19	67.11	82.68	77.59	126.56	222.83
MEDIAN	1.38	1.78	2.15	3.08	2.80	2.44	1.51	0.00	0.00
MINIMUM									
MAXIMUM									

* = Missing sample

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF THE DEMETHYLATED METABOLITE SDZ 86-621
after topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the normal skin in 12 healthy volunteers
(Values below the limit of quantification (0.5 ng/ml) were set to zero)

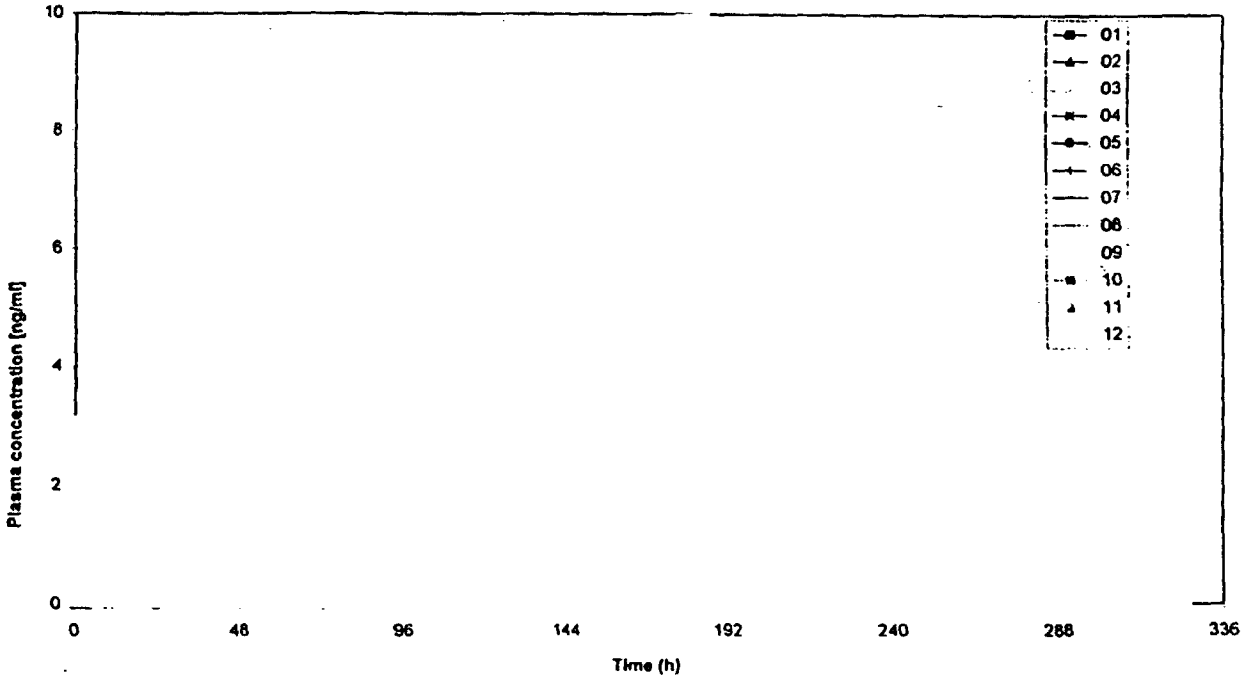
Subject Nr/Time(h)	Mean Daily Dose	0.0	2.0	4.0	10.0	24.0	72.0
	[mg] terbinafine	Day 1					Day 4

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF THE DEMETHYLATED METABOLITE SDZ 86-621
after topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the normal skin in 12 healthy volunteers
(Values below the limit of quantification (0.5 ng/ml) were set to zero)

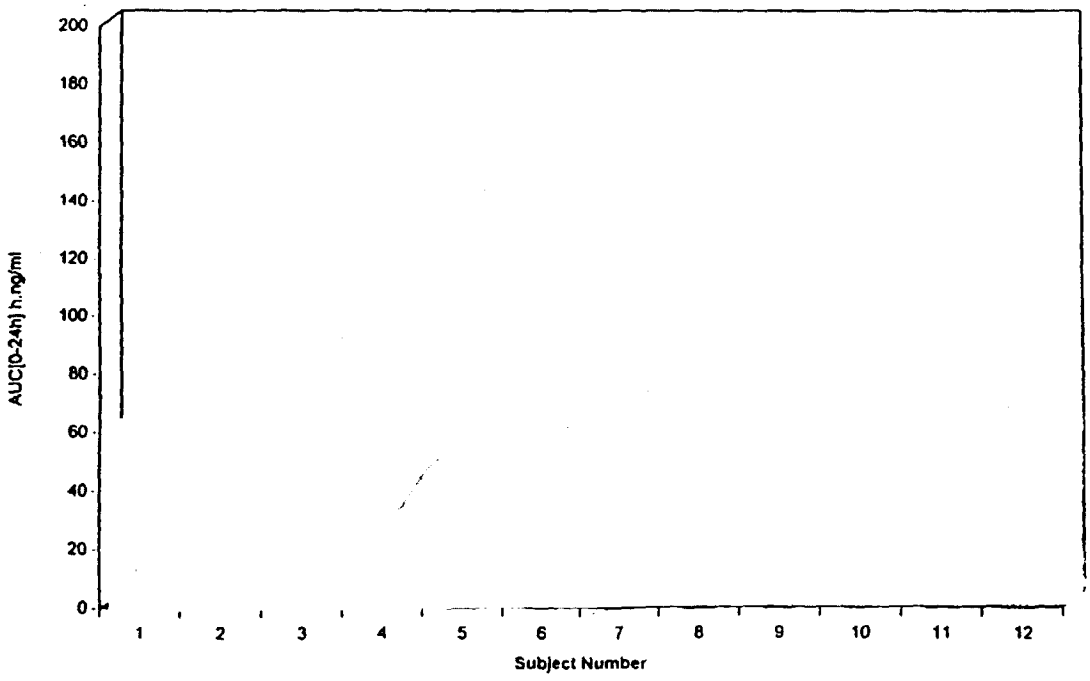
Subject Nr/Time(h)	144.0	146.0	148.0	150.0	154.0	158.0	168.0	192.0	312.0
	Day 7								Day 14
N	12	12	12	12	12	12	12	12	11
MEAN	0.21	0.26	0.31	0.39	0.35	0.43	0.26	0.11	0.00
SD	0.55	0.68	0.76	0.81	0.77	0.61	0.54	0.39	0.00
SEM	0.16	0.20	0.22	0.23	0.22	0.18	0.15	0.11	0.00
CV [%]	257.94	265.84	241.17	206.90	220.68	141.13	204.36	346.41	N.C.
MEDIAN	0.00	0.00	0.00	0.00	0.00	0.25	0.00	0.00	0.00
MINIMUM									
MAXIMUM									

* = Missing sample
N.C.: not calculated

Synoptic view of individual plasma concentrations (ng/ml) of terbinafine (SF 86-327)
after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the normal skin in 12 healthy volunteers
(Values below the limit of quantification (1 ng/ml) were set to zero)



Individual area under the curve (AUC[0-24h]) [h.ng/ml] of terbinafine (SF 86-327) at Day 7
after repeated topical applications of a 1% Lamisil Emulsion gel once daily
for 7 consecutive days to the normal skin in 12 healthy volunteers



NDA/IND#: 20-846 Volume 1.9

Study Type: Bioavailability *Study* # SFW 410-E-00

Study Title: Determination of plasma concentration after repeated application to diseased skin.

Study Site	
Clinical Site	*Analytical Site*

Study Design								
Single Dose	*Multiple Dose*	*Washout Period*	*Cross - over*	*Parallel*	*Other Design*	*Fasted/ Fed*	*FDA Diet*	*No. of fasted hrs.*
	X				Open, not controlled			

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
	X				

Subject Type			
Males		*Females*	
Age	*Weight*	*Age*	*Weight*
(Av 51)	kg (Av 72.0)	(Av 43)	kg (Av 72.0)

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
	12	6	6

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
All	once daily for 7d	Emulsion Gel	1%	Z050 1294
	varied due to			
	diseased area			

Sampling Times

Plasma (8 ml) **Day 1→ 0, 2, 4 10 & 24 hrs, Day 4→ 0 hrs, Day 7→ 0, 2, 4, 6, 10, 14, 24 & 48 hrs**

Assay Method: *Assay Sensitivity:* 1ng/ml Terbinafine, 0. 5ng/ml SDZ86621

Assay Accuracy:[Nominal / measured / %accuracy]; [1 / 1 / 0.1]; [5 /4.75 / 5]; [200 / 213.82 /6.9] for terbinafine

[1 /0.91 / 9.5]; [5 / 4.66 / 6.7]; [200 /200.65 / 2.8] for the metabolite

Labeling Claims From Study: In a study of 12 patients with tinea cruris/corporis, Lamisil DermGel 1% was applied once daily for 7 days to diseased area(s) as well as a 2.5 cm margin of healthy skin. Mean daily application ranged from 20.4 to 92.1 mg. Terbinafine plasma levels were detected in 6 of 12 patients on Day 1 and the maximum level was ng/mL. Terbinafinne plasma levels were measurable in 10 of 12 patients on Day 7 and the maximum concentration was ng/mL. The AUC_{0-24} on Day 7 was 40.5 ng.h/mL

SUBJECT CHARACTERISTICS OF MALE AND FEMALE PATIENTS WITH TINEA CRURIS/CORPORIS

Patient No.	Sex	Age [years]	Weight [kg]	Height [cm]
	Female			
	Female			
	Female			
	Female			
	Male			
	Female			
	Male			
	Male			
	Male			
	Male			
	Female			
	Male			
N	6 Males	12	12.0	12
Median	6 Females	48	74.2	167
Arith.Mean		47	72.0	168
StDev		12	7.4	6
CV [%]		26	10.3	3
SEM		4	2.1	2
Minimum				
Maximum				
L.95%Conf.Lim		39	67.3	165
U.95%Conf.Lim		55	76.7	172

ACTUAL WEIGHT [g] OF 1% LAMISIL^{R} EMULSION GEL APPLIED TO THE DISEASED SKIN IN MALE AND FEMALE PATIENTS WITH TINEA CRURIS/CORPORIS

Patient No.	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Total Amount	Mean
									2.2
									6.0
									9.2
									3.7
									2.2
									2.1
									4.0
									2.4
									3.4
									2.0
									2.1
									3.5

ACTUAL AMOUNT OF TERBINAFINE [mg] APPLIED AS 1% LAMISIL^{R} EMULSION GEL TO THE DISEASED SKIN IN MALE AND FEMALE PATIENTS WITH TINEA CRURIS/CORPORIS

Patient No.	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Total Amount	Mean
									22.0
									60.1
									92.1
									37.3
									21.9
									20.9
									40.1
									23.6
									34.1
									20.4
									21.3
									34.7

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF TERBINAFINE (SF 86-327)
after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the diseased skin in 12 patients with Tinea Cruris/Corporis
(Values below the limit of quantification (1 ng/ml) were set to zero)

Subject Nr/Time(h)	Mean Daily Dose [mg] terbinafine	0.00	2.00	4.00	10.00	24.00	72.00
		Day 1					Day 4
N	12	12	12	12	12	12	12
MEAN	35.71	0.30	0.14	0.38	0.41	0.80	
SD	21.29	0.69	0.48	0.73	0.79	1.14	
SEM	6.15	0.20	0.14	0.21	0.23	0.33	
CV[%]	59.63	234.78	346.41	192.57	191.89	142.11	
MEDIAN	28.85	0.00	0.00	0.00	0.00	0.00	
MINIMUM							
MAXIMUM							

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF TERBINAFINE (SF 86-327)
after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the diseased skin in 12 patients with Tinea Cruris/Corporis
(Values below the limit of quantification (1 ng/ml) were set to zero)

Subject Nr/Time(h)	144.00	146.00	148.00	150.00	154.00	158.00	168.00	192.00	312.00
	Day 7						Day 8	Day 9	Day 14
N	12	12	12	12	12	12	12	12	12
MEAN	1.66	1.58	1.68	1.99	2.03	1.91	0.98	0.52	0.14
SD	1.66	1.50	1.37	1.78	1.80	1.76	1.40	0.79	0.48
SEM	0.48	0.43	0.39	0.52	0.52	0.51	0.40	0.23	0.14
CV[%]	99.60	94.90	81.60	89.80	88.40	91.90	142.98	153.25	346.41
MEDIAN	1.18	1.58	1.62	1.86	2.11	1.70	0.00	0.00	0.00
MINIMUM									
MAXIMUM									

INDIVIDUAL PHARMACOKINETIC PARAMETERS OF TERBINAFINE (SF 86-327) at Day 7
after topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the diseased skin in 12 patients with Tinea Cruris/Corporis

Patient Nr	Cmax [ng/ml]	tmax [h]	AUC[0-24h] [h.ng/ml]	Dose of terbinafine [mg] at Day 7	AUC[0-24h] weighted* [h.ng/ml]
N	12	12	12	12	12
Mean	2.48	7.83	40.54	36.00	41.51
SD	1.85	7.11	36.30	21.06	27.68
SEM	0.53	2.05	10.48	6.08	7.99
CV(%)	74.50	90.70	89.50	58.50	66.70
MEDIAN	2.48	6.00	42.54	28.00	47.85
MINIMUM					
MAXIMUM					

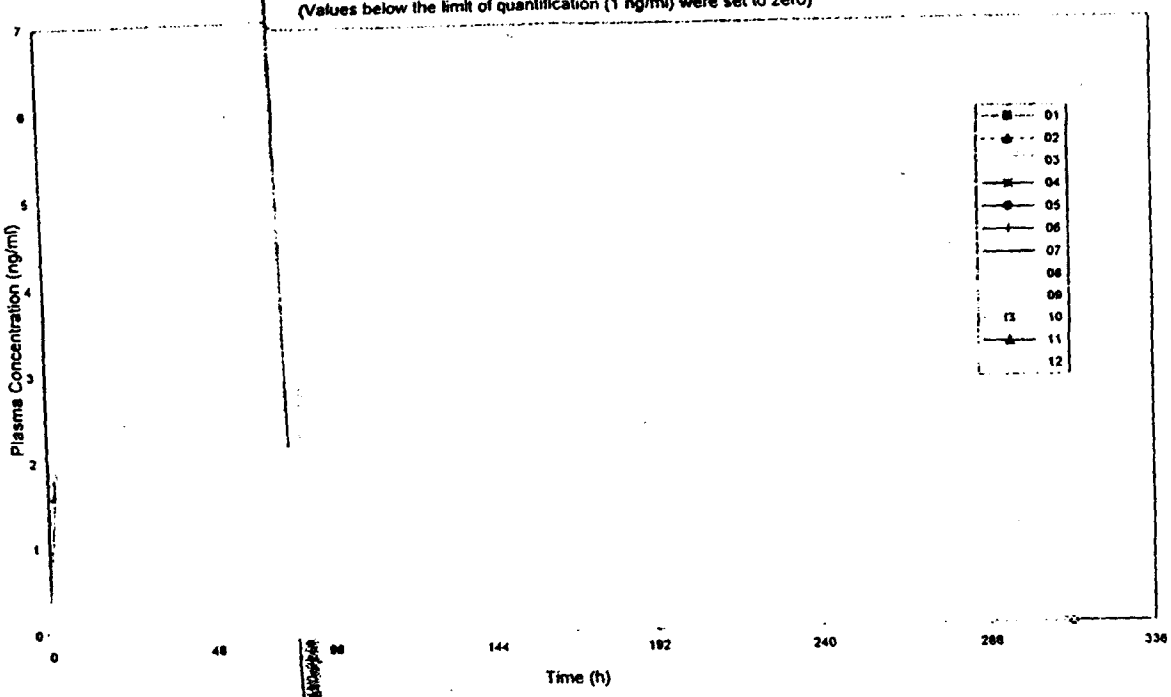
* weighted by the actual individual dose at day 7 relative to the mean dose at day 7

INDIVIDUAL PLASMA CONCENTRATIONS [ng/ml] OF THE DEMETHYLATED METABOLITE SDZ 86-621
after topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days
to the diseased skin in 12 patients with Tinea Cruris/Corporis
(Values below the limit of quantification (0.5 ng/ml) were set to zero)

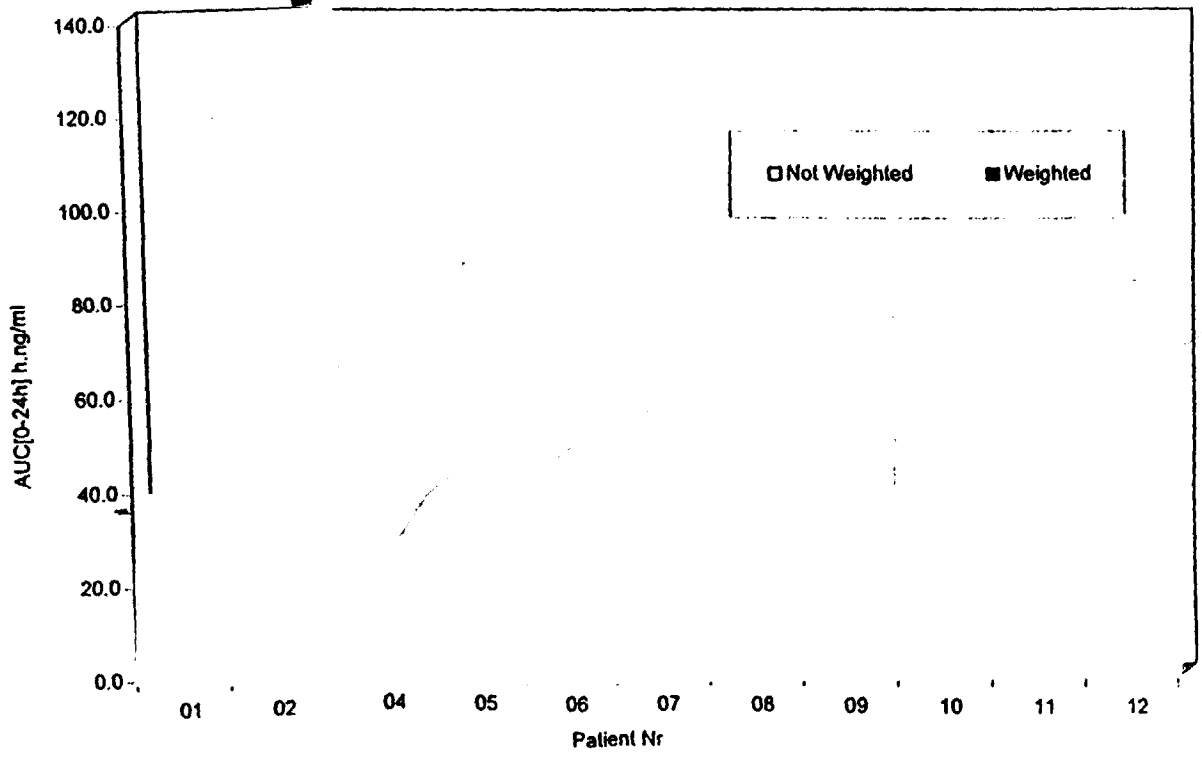
Subject Nr/Time (h)	Mean Daily Dose [mg] terbinafine	0.00	2.00	4.00	10.00	24.00	72.00
		Day 1					Day 4

Subject Nr/Time (h)	144.00	146.00	148.00	150.00	154.00	158.00	168.00	192.00	312.00
	Day 7						Day 8	Day 9	Day 14

Synoptic view of individual plasma concentrations [ng/ml] of terbinafine (SF 86-327) after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days to the diseased skin in 12 patients with Tinea Cruris/Corporis (Values below the limit of quantification (1 ng/ml) were set to zero)



Individual under the curve (AUC[0-24h]) [h.ng/ml] of terbinafine (SF 86-327) at Day 7 after repeated topical applications of a 1% Lamisil Emulsion gel once daily for 7 consecutive days to the diseased skin in 12 patients with Tinea Cruris/Corporis (Weighted AUC [0-24h] with regards to the mean dose administered at Day 7)



NDA/IND#: 20-846 Volume 1.10

Study Type: Bioavailability *Study* # SFG 205-E-00

Study Title: Bioavailability comparison of terbinafine 1% gel vs. 1% cream.

Study Site	
Clinical Site	*Analytical Site*

Study Design								
Single Dose	*Multiple Dose*	*Washout Period*	*Cross - over*	*Parallel*	*Other Design*	*Fasted/ Fed*	*FDA Diet*	*No. of fasted hrs.*
	X			X	Open, not controlled	NA		

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X					

Subject Type			
Males		*Females*	
Age	*Weight*	*Age*	*Weight*
	kg		kg

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
gel-1 day	6	3	3
gel-5 days	6	3	3
gel-7 days	6	3	3
cream-1 day	6	3	3
cream-5 days	6	3	3
cream-7 days	6	3	3

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
gel -1, 5, 7 days	0.5 gm	Emulsion Gel	1%	Z028 1291
cream-1,5,7 days	0.5 gm	Cream	1%	Z064 0690

Skin Sampling Times

Day 1(all) prior to dosing and 4, 8, 12, 24, 48, 72, 96 and 168 hrs (7 days) after last dose

Day 3&5 prior to dosing on days 3&5and 4, 8, 12, 24, 48, 72, 96 and 168 hrs after last dose on day 5

Day 7 prior to dosing and 4, 8, 12, 24, 48, 72, 96 and 168 hrs (7 days) after last dose

Assay Method: *Assay Sensitivity:*7.3 ng/ssb (0.18ng/cm^2)

Assay Accuracy:[Nominal/measured/%accuracy]; [12.5/ 12.67 / 7.5]; [250 / 260.82 / 10.6]; [1000 / 1113.52 / 6.3] for terbinafine

Labeling Claims: The total stratum corneum AUC_{0-t} for Lamisil® DermGel™ was significantly greater ($p < 0.05$) than that seen for Lamisil Cream 1% after 1 and 5 days of application. After 7 days of application there was no difference in AUC_{0-t} between the formulations. The total stratum corneum $t_{1/2}$ for terbinafine after Day 7 application of Lamisil® DermGel™ was 27.2 h vs. 35.2 h for Lamisil Cream 1% ($p < 0.05$).

Summary of Level 1 Stratum Corneum Pharmacokinetic Parameters: AUC 0-t (ng.hr/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	3238.100	3780.403	4807.130	3376.447	3533.783	5446.440
Median	3358.790	3817.760	4732.290	3385.890	3556.210	5517.820
s.d.	490.4198	280.9984	443.7165	345.7646	228.9598	287.7103
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	0.95	(0.85, 1.07)	0.409	
	5 days	1.07	(0.95, 1.20)	0.258	
	7 days	0.88	(0.78, 0.99)	0.036	*
Lamisil Gel:	1 day vs. 5 days	0.85	(0.75, 0.96)	0.008	**
	1 day vs. 7 days	0.67	(0.59, 0.75)	<0.001	***
	5 days vs. 7 days	0.79	(0.70, 0.89)	<0.001	***
Lamisil Cream:	1 day vs. 5 days	0.95	(0.85, 1.07)	0.414	
	1 day vs. 7 days	0.62	(0.55, 0.70)	<0.001	***
	5 days vs. 7 days	0.65	(0.58, 0.73)	<0.001	***

Summary of Level 1 Stratum Corneum Pharmacokinetic Parameters: Cmax (ng/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	242.778	357.865	356.580	281.547	290.965	357.613
Median	238.950	360.960	353.820	283.665	284.980	338.670
s.d.	32.9948	43.3623	43.5101	35.2779	31.5027	51.1255
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	0.86	(0.75, 1.00)	0.046	*
	5 days	1.23	(1.06, 1.42)	0.007	**
	7 days	1.00	(0.86, 1.16)	0.985	
Lamisil Gel:	1 day vs. 5 days	0.68	(0.59, 0.78)	<0.001	***
	1 day vs. 7 days	0.68	(0.59, 0.79)	<0.001	***
	5 days vs. 7 days	1.00	(0.87, 1.16)	0.961	
Lamisil Cream:	1 day vs. 5 days	0.97	(0.83, 1.12)	0.627	
	1 day vs. 7 days	0.79	(0.68, 0.91)	0.002	**
	5 days vs. 7 days	0.82	(0.71, 0.94)	0.008	**

Summary of Level 1 Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	n/a	5	6	n/a	6	6
Mean		19.38	33.42		20.14	43.21
Median		19.43	35.54		19.53	46.19
s.d.		1.862	14.138		3.971	9.261
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	n/a	n/a	n/a	
	5 days	-0.75	(-12.09, 10.59)	0.891	
	7 days	-9.79	(-20.60, 1.02)	0.073	(*)
Lamisil Gel:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	-14.04	(-25.38, -2.70)	0.018	*
Lamisil Cream:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	-23.08	(-33.89, -12.27)	<0.001	***

Summary of Level 2 Stratum Corneum Pharmacokinetic Parameters: AUC 0-t (ng.hr/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	2384.973	2373.490	3061.137	2065.163	2284.827	3025.800
Median	2438.690	2327.750	3126.340	2027.370	2305.510	3023.180
s.d.	256.2306	225.7166	216.5734	348.0628	93.5922	70.3278
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	1.16	(1.04, 1.31)	0.012	*
	5 days	1.04	(0.92, 1.16)	0.539	
	7 days	1.01	(0.90, 1.13)	0.865	
Lamisil Gel:	1 day vs. 5 days	1.00	(0.89, 1.13)	0.949	
	1 day vs. 7 days	0.78	(0.69, 0.87)	<0.001	***
	5 days vs. 7 days	0.77	(0.69, 0.87)	<0.001	***
Lamisil Cream:	1 day vs. 5 days	0.89	(0.80, 1.00)	0.056	(*)
	1 day vs. 7 days	0.67	(0.60, 0.76)	<0.001	***
	5 days vs. 7 days	0.75	(0.67, 0.85)	<0.001	***

Summary of Level 2 Stratum Corneum Pharmacokinetic Parameters: Cmax (ng/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	201.240	222.120	247.383	183.200	212.162	265.695
Median	199.175	221.100	249.135	185.325	207.850	259.970
s.d.	20.2538	35.8433	22.4068	23.9846	24.3447	29.4006
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	1.10	(0.96, 1.27)	0.173	
	5 days	1.04	(0.90, 1.20)	0.567	
	7 days	0.93	(0.81, 1.07)	0.322	
Lamisil Gel:	1 day vs. 5 days	0.91	(0.79, 1.05)	0.196	
	1 day vs. 7 days	0.81	(0.71, 0.94)	0.006	**
	5 days vs. 7 days	0.89	(0.77, 1.03)	0.107	
Lamisil Cream:	1 day vs. 5 days	0.86	(0.75, 0.99)	0.041	*
	1 day vs. 7 days	0.69	(0.60, 0.79)	<0.001	***
	5 days vs. 7 days	0.80	(0.69, 0.92)	0.003	**

Summary of Level 2 Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	n/a	6	6	n/a	3	6
Mean		18.45	30.68		26.25	44.99
Median		18.79	27.33		23.45	45.19
s.d.		2.365	9.713		5.645	13.545
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value	
Lamisil Gel vs Cream:	1 day	n/a	n/a	n/a	
	5 days	-7.79	(-21.72, 6.13)	0.254	
	7 days	-14.31	(-25.68, -2.94)	0.017	*
Lamisil Gel:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	-12.23	(-23.59, -0.86)	0.037	*
Lamisil Cream:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	-18.74	(-32.67, -4.82)	0.011	*

Summary of Level 3 Stratum Corneum Pharmacokinetic Parameters: AUC 0-t (ng.hr/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	1379.030	1776.780	2148.860	1001.947	1346.963	1831.763
Median	1297.940	1754.870	2148.130	1057.850	1340.290	1837.350
s.d.	189.7754	106.1386	141.8106	168.5783	93.9240	126.2773
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value
Lamisil Gel vs. Cream:	1 day	1.38	(1.22, 1.57)	<0.001 ***
	5 days	1.32	(1.16, 1.50)	<0.001 ***
	7 days	1.17	(1.04, 1.33)	0.014 *
Lamisil Gel:	1 day vs. 5 days	0.77	(0.68, 0.87)	<0.001 ***
	1 day vs. 7 days	0.64	(0.56, 0.72)	<0.001 ***
	5 days vs. 7 days	0.83	(0.73, 0.94)	0.004 **
Lamisil Cream:	1 day vs. 5 days	0.74	(0.65, 0.83)	<0.001 ***
	1 day vs. 7 days	0.54	(0.48, 0.61)	<0.001 ***
	5 days vs. 7 days	0.74	(0.65, 0.83)	<0.001 ***

Summary of Level 3 Stratum Corneum Pharmacokinetic Parameters: Cmax (ng/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	116.935	156.533	160.283	126.903	134.757	193.892
Median	116.715	154.475	157.105	127.580	136.215	190.560
s.d.	10.4637	19.4843	20.5212	21.2251	11.8680	19.1028
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value
Lamisil Gel vs. Cream:	1 day	0.93	(0.81, 1.07)	0.306
	5 days	1.16	(1.00, 1.33)	0.043 *
	7 days	0.82	(0.72, 0.95)	0.009 **
Lamisil Gel:	1 day vs. 5 days	0.75	(0.65, 0.86)	<0.001 ***
	1 day vs. 7 days	0.73	(0.63, 0.84)	<0.001 ***
	5 days vs. 7 days	0.98	(0.85, 1.13)	0.735
Lamisil Cream:	1 day vs. 5 days	0.93	(0.81, 1.08)	0.325
	1 day vs. 7 days	0.65	(0.56, 0.75)	<0.001 ***
	5 days vs. 7 days	0.70	(0.60, 0.80)	<0.001 ***

Summary of Level 3 Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	n/a	5	6	n/a	1	2
Mean		24.78	31.64		31.39	37.09
Median		26.23	29.86		31.39	37.09
s.d.		3.625	8.999			16.686
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value
Lamisil Gel vs. Cream:	1 day	n/a	n/a	n/a
	5 days	n/a	n/a	n/a
	7 days	n/a	n/a	n/a
Lamisil Gel:	1 day vs. 5 days	n/a	n/a	n/a
	1 day vs. 7 days	n/a	n/a	n/a
	5 days vs. 7 days	-6.86	(-16.62, 2.91)	0.147
Lamisil Cream:	1 day vs. 5 days	n/a	n/a	n/a
	1 day vs. 7 days	n/a	n/a	n/a
	5 days vs. 7 days	n/a	n/a	n/a

Summary of Level 4 Stratum Corneum Pharmacokinetic Parameters: AUC 0-t (ng.hr/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	763.220	1151.623	1406.537	522.427	658.677	858.347
Median	771.720	1159.440	1401.800	560.800	646.930	857.610
s.d.	51.8302	170.0573	84.0143	160.9439	72.8074	51.2350
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	1.54	(1.25, 1.89)	<0.001	***
	5 days	1.74	(1.41, 2.15)	<0.001	***
	7 days	1.64	(1.33, 2.02)	<0.001	***
Lamisil Gel:	1 day vs. 5 days	0.67	(0.54, 0.82)	<0.001	***
	1 day vs. 7 days	0.54	(0.44, 0.67)	<0.001	***
	5 days vs. 7 days	0.81	(0.66, 1.00)	0.051	(*)
Lamisil Cream:	1 day vs. 5 days	0.76	(0.61, 0.93)	0.011	*
	1 day vs. 7 days	0.58	(0.47, 0.71)	<0.001	***
	5 days vs. 7 days	0.76	(0.62, 0.94)	0.014	*

Summary of Level 4 Stratum Corneum Pharmacokinetic Parameters: Cmax (ng/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	76.433	97.782	98.718	81.513	70.760	97.277
Median	74.375	104.550	99.815	88.760	69.860	92.605
s.d.	7.3986	15.6803	13.1155	25.0984	10.0487	12.4564
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	0.99	(0.78, 1.25)	0.913	
	5 days	1.38	(1.08, 1.75)	0.011	*
	7 days	1.01	(0.80, 1.29)	0.906	
Lamisil Gel:	1 day vs. 5 days	0.79	(0.62, 1.00)	0.051	(*)
	1 day vs. 7 days	0.78	(0.61, 0.99)	0.040	*
	5 days vs. 7 days	0.99	(0.78, 1.25)	0.907	
Lamisil Cream:	1 day vs. 5 days	1.10	(0.86, 1.40)	0.427	
	1 day vs. 7 days	0.80	(0.63, 1.01)	0.064	(*)
	5 days vs. 7 days	0.73	(0.57, 0.92)	0.011	*

Summary of Level 4 Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	n/a	3	6	n/a	n/a	n/a
Mean		28.32	40.43			
Median		27.08	40.11			
s.d.		3.154	4.379			
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	n/a	n/a	n/a	
	5 days	n/a	n/a	n/a	
	7 days	n/a	n/a	n/a	
Lamisil Gel:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	-12.12	(-18.92, -5.32)	0.004	**
Lamisil Cream:	1 day vs. 5 days	n/a	n/a	n/a	
	1 day vs. 7 days	n/a	n/a	n/a	
	5 days vs. 7 days	n/a	n/a	n/a	

Table 3.6.2.1
Summary of Level 5 Stratum Corneum Pharmacokinetic Parameters: AUC 0-t (ng.hr/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)
N	6	6	6	6	6	6
Mean	472.910	738.527	855.657	248.180	355.987	315.473
Median	484.880	718.300	844.760	251.520	344.480	322.500
s.d.	158.5715	103.8373	188.2127	87.2868	38.4823	22.409
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	1.92	(1.42, 2.60)	<0.001	***
	5 days	2.07	(1.53, 2.80)	<0.001	***
	7 days	2.66	(1.97, 3.60)	<0.001	***
Lamisil Gel:	1 day vs. 5 days	0.61	(0.45, 0.83)	0.002	**
	1 day vs. 7 days	0.54	(0.40, 0.72)	<0.001	***
	5 days vs. 7 days	0.88	(0.65, 1.18)	0.375	
Lamisil Cream:	1 day vs. 5 days	0.66	(0.49, 0.89)	0.008	**
	1 day vs. 7 days	0.74	(0.55, 1.00)	0.052	(*)
	5 days vs. 7 days	1.13	(0.83, 1.52)	0.431	

Summary of Level 5 Stratum Corneum Pharmacokinetic Parameters: Cmax (ng/cm2)
(Population: Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Day (N=6)
N	6	6	6	6	6	6
Mean	48.645	58.210	52.612	44.535	37.352	29.54
Median	51.145	54.860	52.925	41.670	37.955	27.17
s.d.	14.0936	8.4314	11.1038	18.8379	5.5071	6.00
Minimum						
Maximum						

Comparison		Geometric Mean Ratio	95% Confidence Interval	p-value	
Lamisil Gel vs. Cream:	1 day	1.15	(0.83, 1.58)	0.383	
	5 days	1.56	(1.13, 2.15)	0.008	**
	7 days	1.77	(1.29, 2.44)	<0.001	***
Lamisil Gel:	1 day vs. 5 days	0.81	(0.59, 1.12)	0.197	
	1 day vs. 7 days	0.91	(0.66, 1.25)	0.552	
	5 days vs. 7 days	1.12	(0.81, 1.54)	0.478	
Lamisil Cream:	1 day vs. 5 days	1.10	(0.80, 1.52)	0.531	
	1 day vs. 7 days	1.41	(1.02, 1.93)	0.038	*
	5 days vs. 7 days	1.27	(0.92, 1.75)	0.134	

Summary of Level 5 Stratum Corneum Pharmacokinetic Parameters: t1/2 (hrs) (Page 6 of 6)
Population: (Evaluable Subjects)

	Treatment Group					
	Lamisil Gel			Lamisil Cream		
	One Day (N=6)	Five Days (N=6)	Seven Days (N=6)	One Day (N=6)	Five Days (N=6)	Seven Day (N=6)
N	n/a	n/a	5	n/a	n/a	n/a
Mean			53.25			
Median			50.41			
s.d.			11.911			
Minimum						
Maximum						

Comparison		Mean Difference	95% Confidence Interval	p-value
Lamisil Gel vs. Cream:	1 day	n/a	n/a	n/a
	5 days	n/a	n/a	n/a
	7 days	n/a	n/a	n/a
Lamisil Gel:	1 day vs. 5 days	n/a	n/a	n/a
	1 day vs. 7 days	n/a	n/a	n/a
	5 days vs. 7 days	n/a	n/a	n/a
Lamisil Cream:	1 day vs. 5 days	n/a	n/a	n/a
	1 day vs. 7 days	n/a	n/a	n/a
	5 days vs. 7 days	n/a	n/a	n/a

NDA/IND#: 20-846 Volume 1.11

Study Type: Bioavailability *Study* # SFG 205-E-00

Study Title: Bioavailability comparison of terbinafine 1% gel with oral placebo vs. 1% gel co-administered with oral tablets.

Study Site	
Clinical Site	*Analytical Site*
	Not mentioned

Study Design								
Single Dose	*Multiple Dose*	*Washout Period*	*Cross-over*	*Parallel*	*Other Design*	*Fasted/ Fed*	*FDA Diet*	*No. of fasted hrs.*
	X (for 1 week)			X	randomized double-blind	NA		

Subject Category					
Normal	*Patients*	*Young*	*Elderly*	*Renal*	*Hepatic*
X					

Subject Type			
Males		*Females*	
Age	*Weight*	*Age*	*Weight*

Subject Treatment Group			
Group No.	*Total No.*	*Males*	*Females*
gel+oral placebo	12	12	
gel+oral tablet	12	12	

Treatment Group	*Dose*	*Dosage Form*	*Strength*	*Lot #*
gel+oral placebo	50-60 mg/day		1%+ placebo	Z028 1991 & 016 0992
gel+oral tablet			1% +250 mg	Z028 1991 & 016 0992

Plasma & Tissue Sampling Times

Day 0 and Days 1, 2, 6, 12, 24, 36, 48 and 54 after cessation of application

Assay Method: *Assay Sensitivity:* 9.3ng/ml for plasma, 24.9ng/10mg for dermis-epidermis, 2.8 ng/10mg for stratum corneum from the back and 47ng/10mg for stratum corneum from the footsoles.

Assay Accuracy:[Nominal/measured/% CV]; [715/668/5]; [186/192/6]; [24.88/24.7/8/3] for terbinafine in plasma. [373/356/14]; [124/95/10.6]; 12.44/12.94/24.1]; [4.35/6.63/12.8] for terbinafine in biopsies %CV (131) high for lower concentrations in stratum (foot sole); %CV <12.9 for all samples.

Labeling claims from this study: None from this study.

TABLE 1

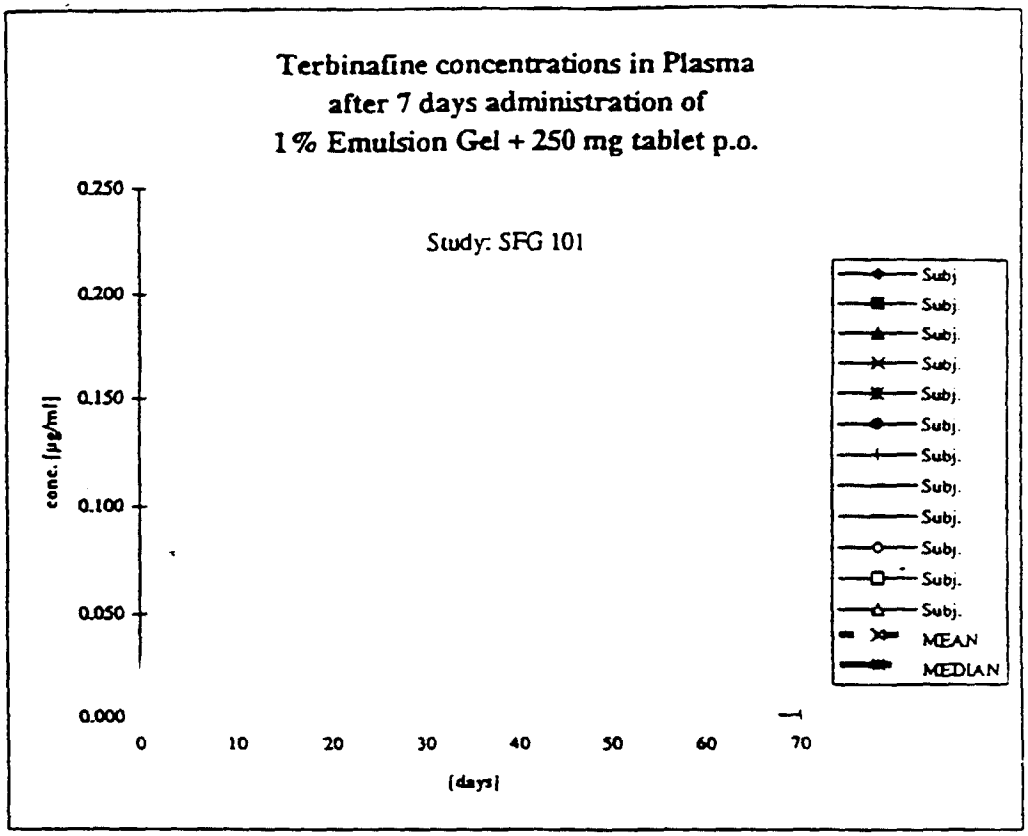
Study: SFG 101

Terbinafine concentrations in Plasma after 7 days administration of 1% Emulsion Gel or 250 mg p.o. + 1% Gel

Time [days] ->	0	8	9	13	19	31	43	55	61
Subject No:	[µg/ml]								
[redacted]									
Topical:	empty values: no sample or sample loss								
MEAN	0	0	0	0	0	0	0	0	0
StDEV									
CV[%]									
MEDIAN	0	0	0	0	0	0	0	0	0
Combined:									
[redacted]	0	0.106	0.071	0.043	0.024	0.012	0.005	0.002	0.000
StDEV	0	0.056	0.041	0.022	0.014	0.011	0.007	0.004	0.000
CV[%]	0	52.4	57.7	50.4	59.3	87.9	158.6	222.8	#DIV/0!
MEDIAN	0	0.179	0.089	0.062	0.037	0.013	0.000	0.000	0.000

	Topical	Combined
MEAN AUC(8-61d) [µg*days/ml]	0	0.9
Cmax of the MEAN [µg/ml]	0	0.106
tmax of the MEAN [days]		8
MEDIAN AUC(8-61d) [µg*days/ml]	0	0.9

FIGURES 1 AND 2



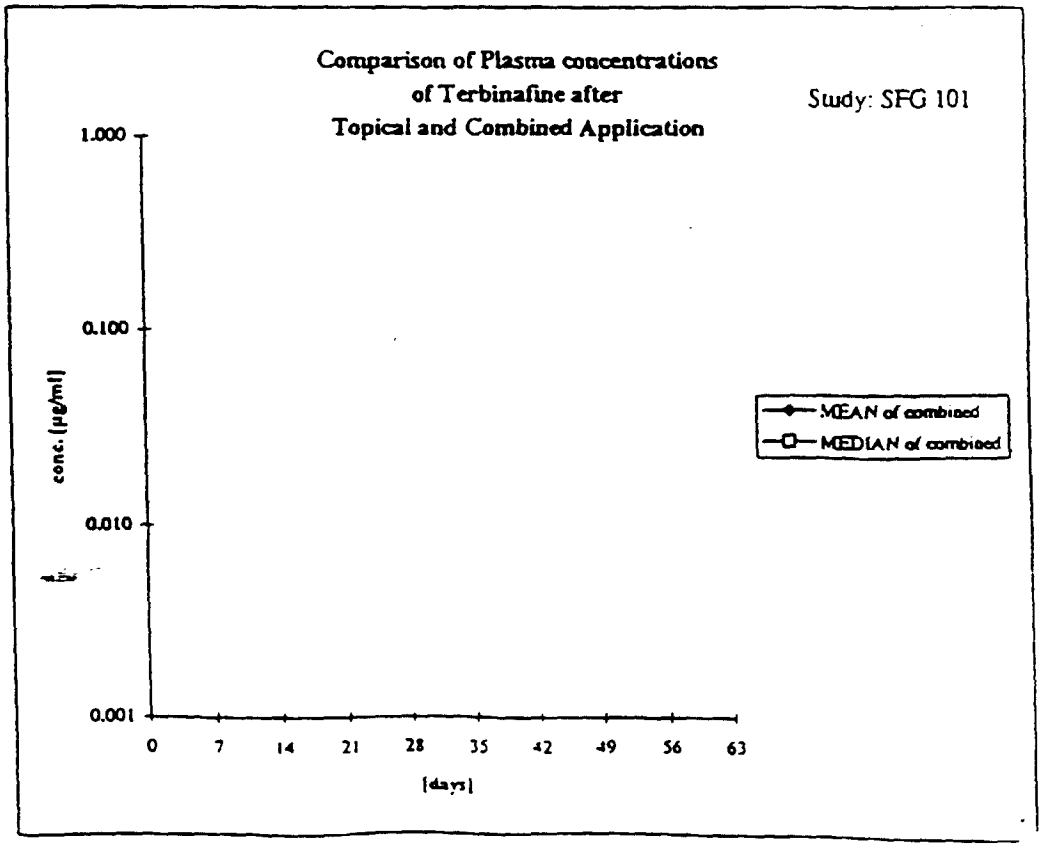
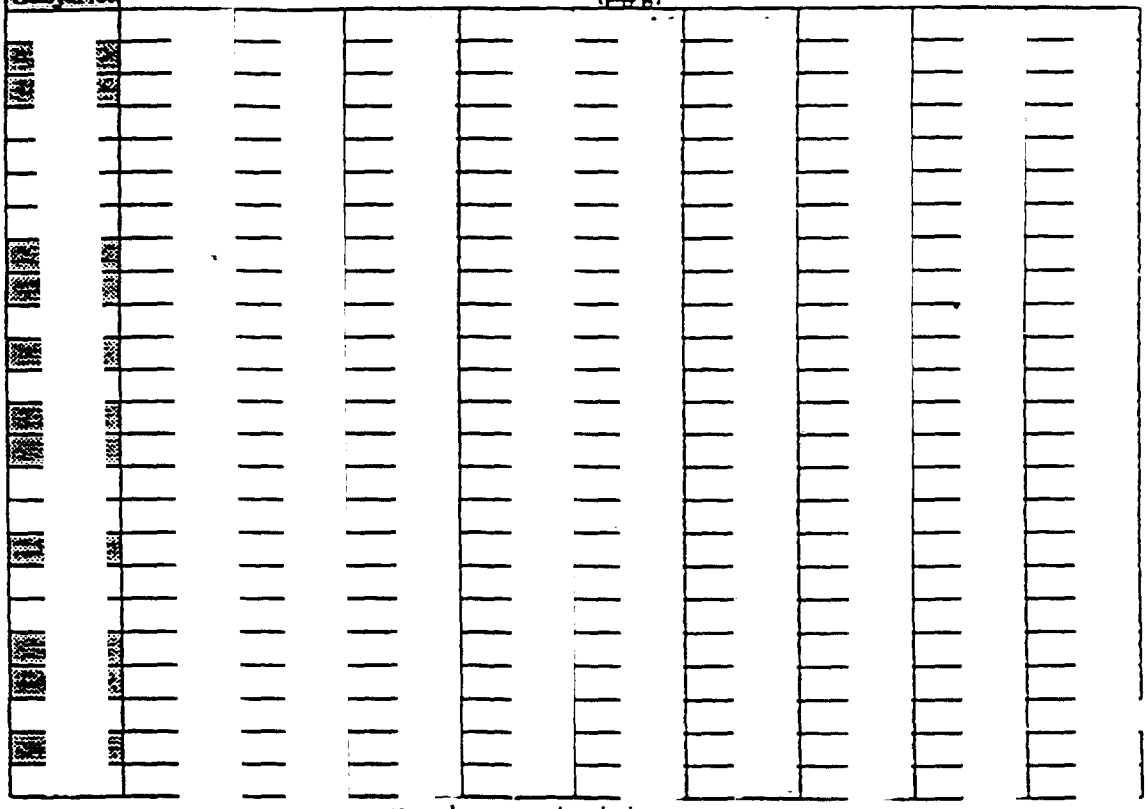


TABLE 2

Study: SFG 101 Terbinafine concentrations in Stratum corneum (from the back) after 7 days administration of 1% Emulsion Gel or 250 mg p.o. + 1% Gel

(* Subject 7 excluded from statistics)

Day ->	0	8	9	13	19	31	43	55	61
Subj.-No.	conc. [µg/g]								



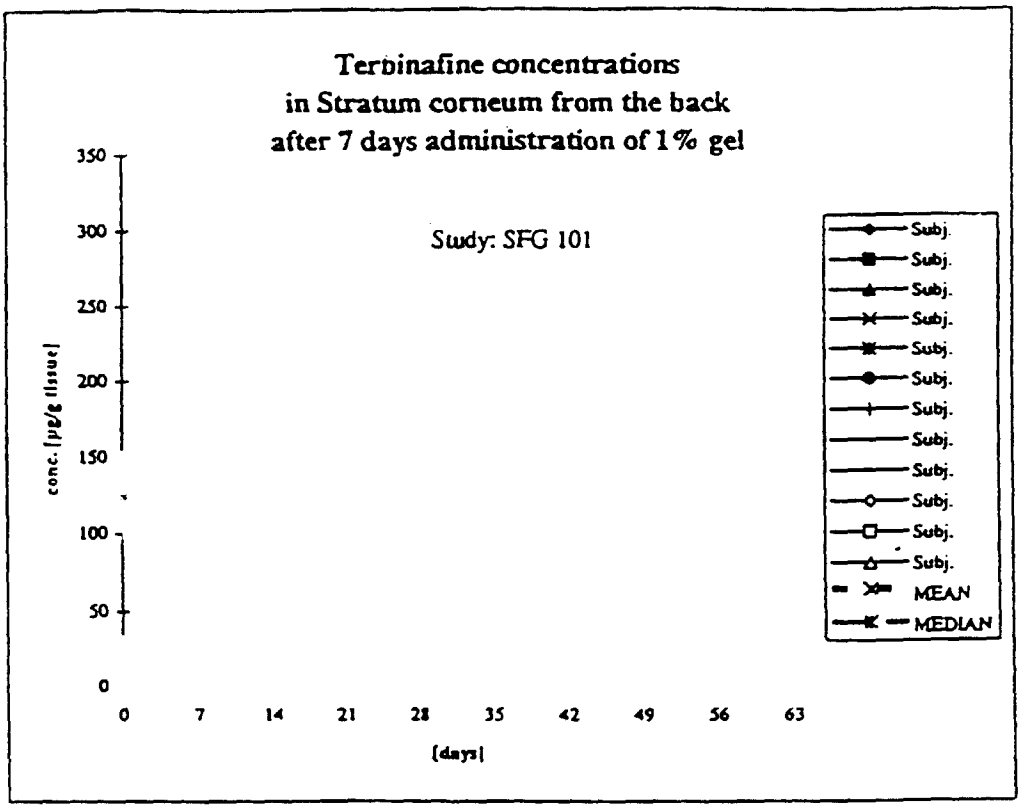
empty values: sample missing

Topical:									
MEAN	0	67.9	84.6	32.2	16.9	4.3	4.1	4.6	0.8
StDev	0	73	107	32	25	10	12	12	2
CV[%]	0	107	126	100	146	230	293	269	218
MEDIAN	0	44.7	33.8	20.8	4.5	0.6	0.5	0.0	0.0

Combined:									
MEAN	0	96.4	39.1	11.5	8.8	5.9	7.4	0.8	2.4
StDev	0	74	26	10	20	13	19	2	4
CV[%]	#DIV/0!	77	65	91	222	226	259	226	168
MEDIAN	0	78.6	28.4	9.2	1.2	1.0	0.0	0.0	0.7

	Topical	Combined
MEAN AUC(8-61d) [µg*days/g]	703.1	457.0
Cmax (µg/g) of the MEAN	85	96
tmax (days) of the MEAN	9	8
MEDIAN AUC (8-61d) [µg*days/g]	706.6	370.0
N	12	11

FIGURES 3 AND 4



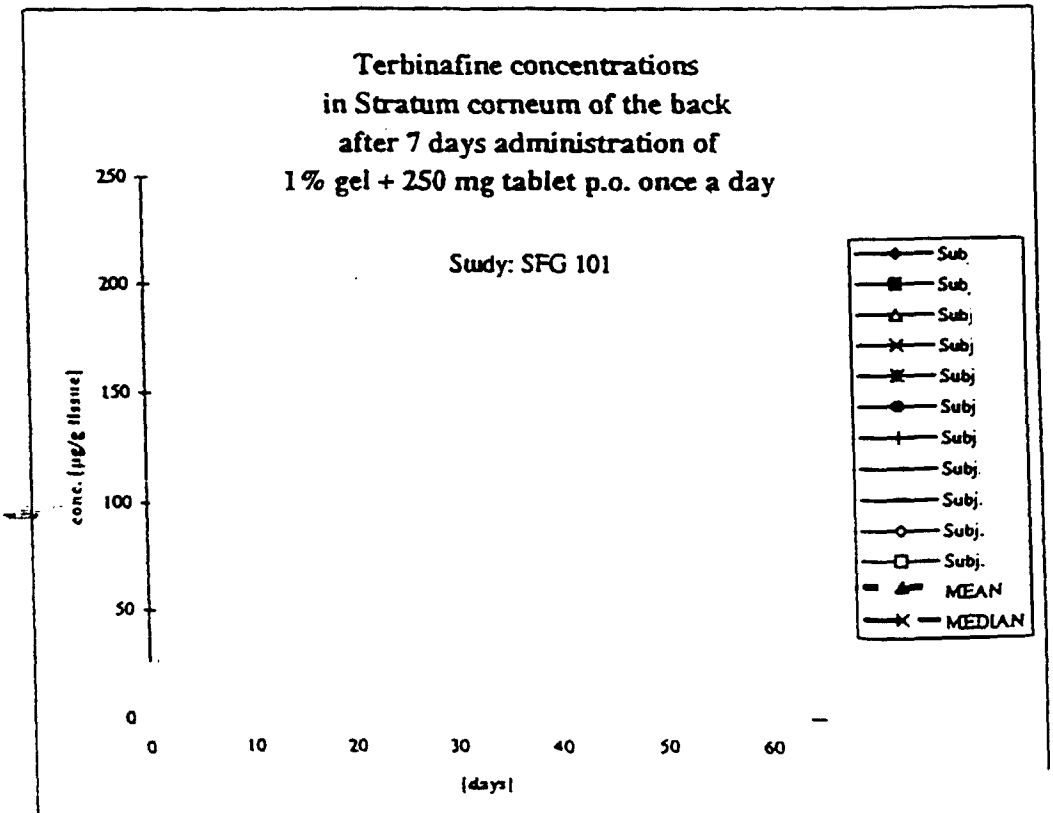


TABLE 3

Study: SFG 101 **Terbinafine concentrations in Stratum corneum (from the foot sole) after 7 days administration of 1% Emulsion Gel or 250 mg p.o. + 1% Gel**

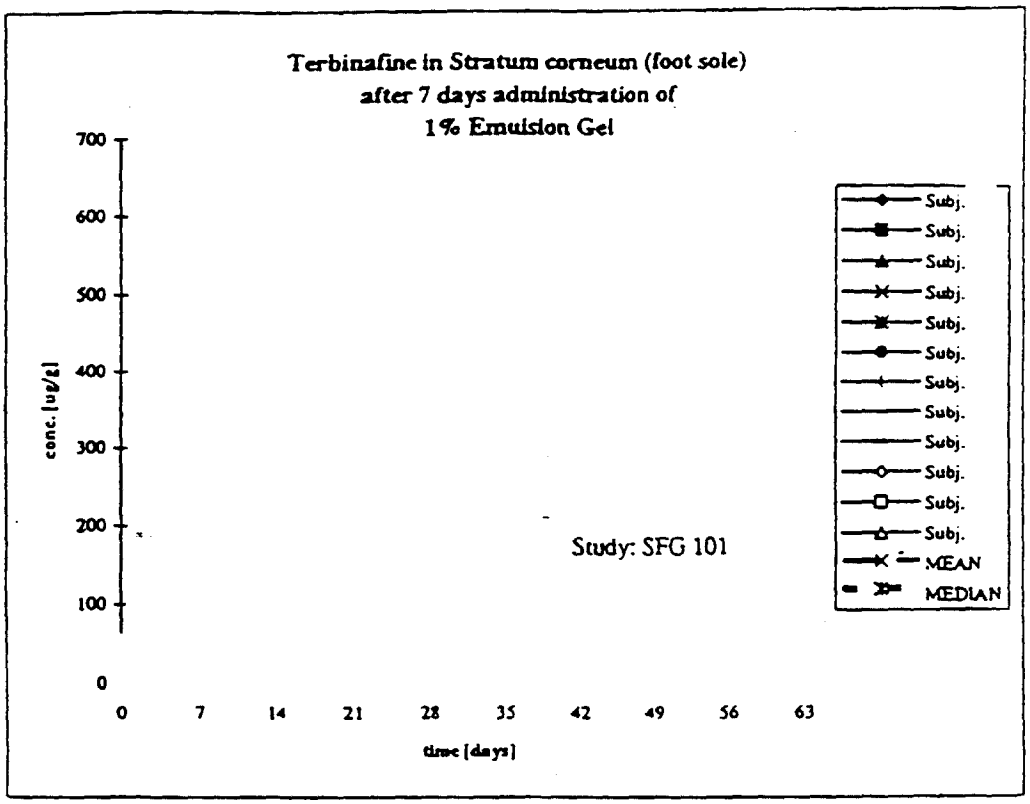
Day ->	0	8	9	13	19	31	43	55	61
Subj. No.				conc. [µg/g]					
[redacted]									

empty values: no sample available

Topical:									
MEAN	0	211.7	75.9	20.7	8.0	3.0	0.0	0.0	0.0
StDEV	0	244.1	93.2	19.4	14.3	4.7	0.0	0.0	0.0
CV(%)	0	115.3	122.8	93.4	178.2	154.4	0.0	0.0	0.0
MEDIAN	0	123.0	38.8	15.5	0.0	0.0	0.0	0.0	0.0
Combined:									
MEAN	0	186.2	209.2	86.7	12.6	5.3	2.2	2.1	1.9
StDEV	0	121.8	186.2	127.0	20.1	7.4	4.4	7.4	3.6
CV(%)	0	65.4	89.0	146.4	159.6	138.5	203.1	346.4	186.7
MEDIAN	0	156.8	109.2	40.6	0.0	0.0	0.0	0.0	0.0

	Topical	Combined
MEAN AUC (8-61d) [µg*days/g]	507.8	1277.8
Cmax [µg/g] of the MEAN	211.7	209.2
tmax [days] of the MEAN	8	9
MEDIAN AUC (8-61d) [µg*days/g]	386.8	914.3
N	12	12

FIGURES 5 AND 6



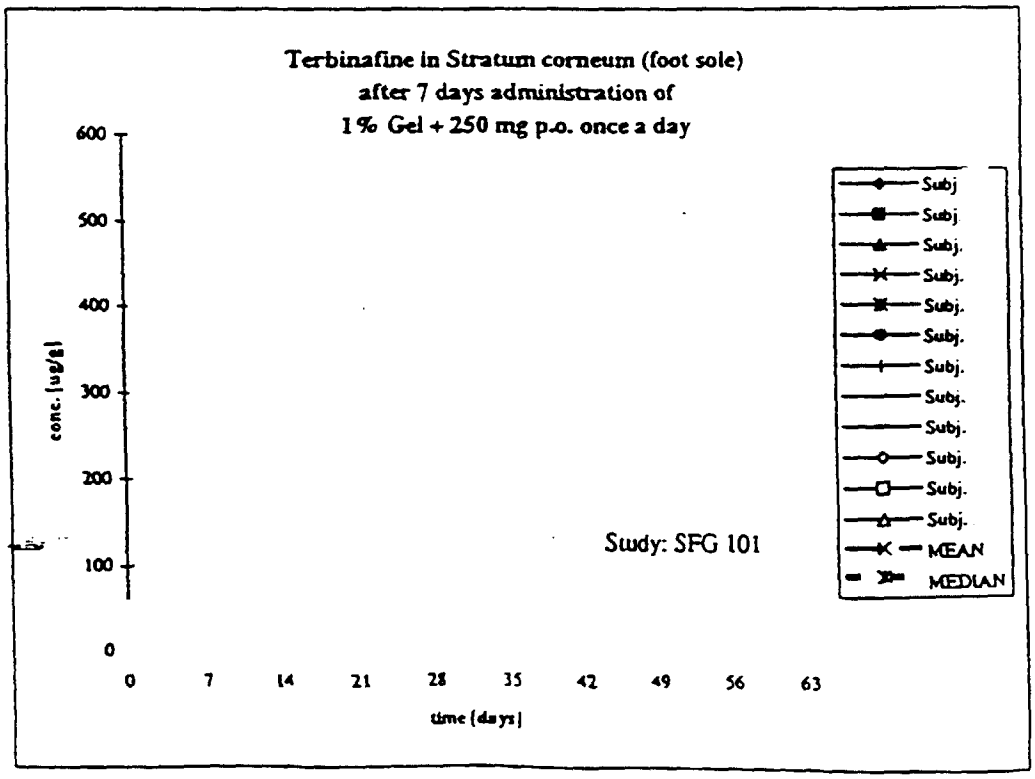


TABLE 4

Study: SFG 101

Terbinafine concentrations in Dermis-epidermis
after 7 days administration of
1% Emulsion Gel or 250 mg p.o. + 1% Gel

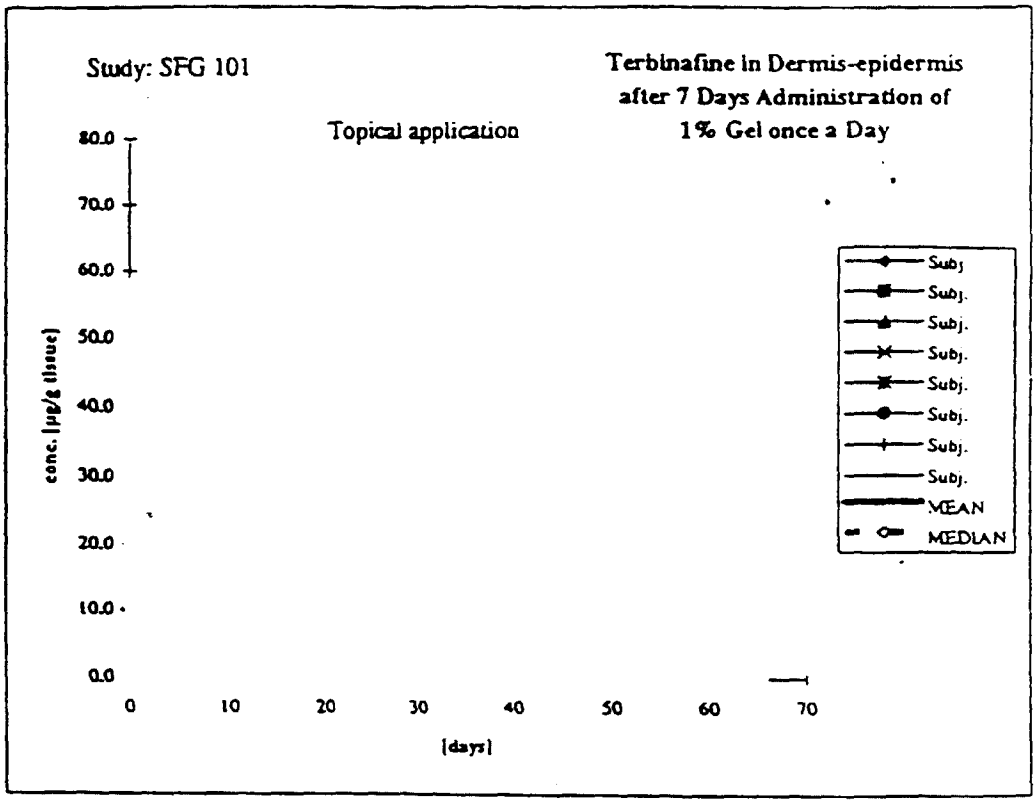
Day =>	0	8	9	13	19	31	43	55	61
Subj. No.	conc. [µg/g]								
[redacted]									

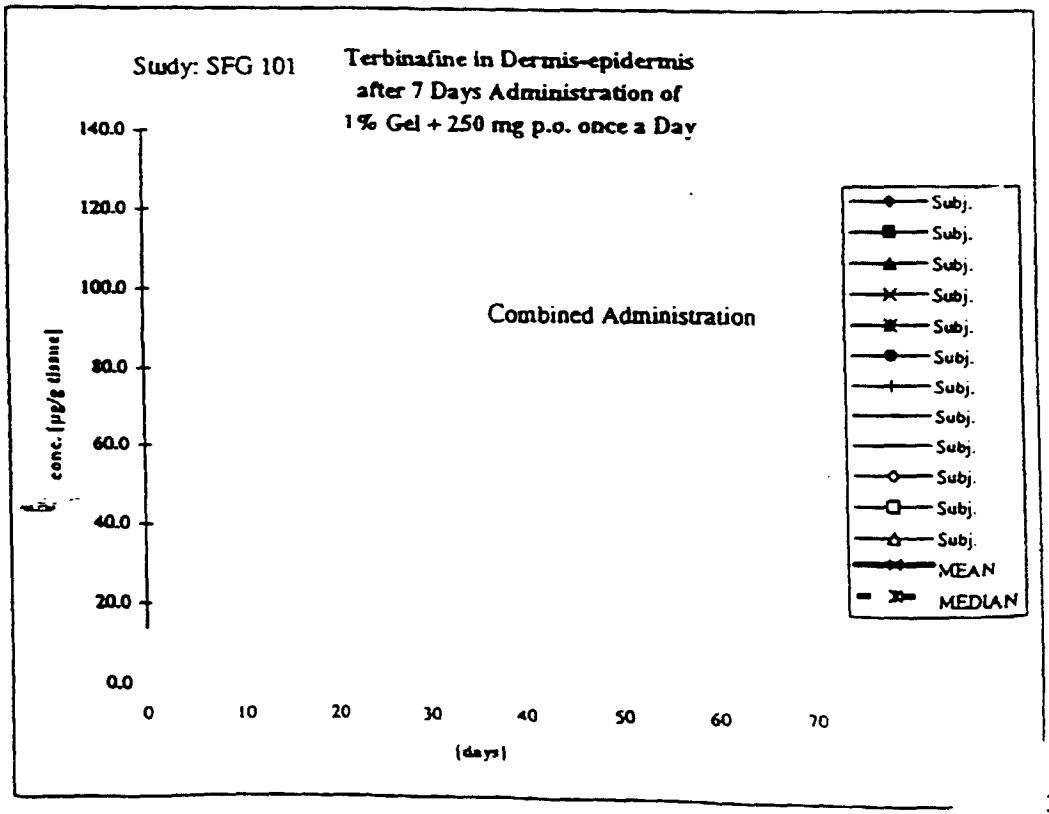
Topical:									
MEAN	9.9	17.4	17.6	2.2	1.4	9.7	5.5	6.2	7.8
StDev	18.0	24.0	24.0	5.1	2.8	21.4	9.0	20.2	20.1
CV[%]	182.1	137.5	136.0	229.4	200.7	221.7	165.1	325.6	258.7
MEDIAN	0.0	7.9	1.8	0.0	0.0	0.0	0.0	0.0	0.0

Combined:									
MEAN	1.2	42.2	14.0	1.8	22.4	11.8	11.1	1.6	1.0
StDev	2.2	25.1	17.1	4.2	43.1	20.9	17.5	5.6	2.5
CV[%]	183.4	59.5	121.9	241.3	192.4	176.6	157.5	346.3	239.4
MEDIAN	0.0	39.3	13.0	0.0	0.0	0.0	0.0	0.0	0.0

	Topical	Combined
MEAN AUC(8-61d) [µg*days/g]	336.8	559.8
MEAN Cmax [µg/g]	17.6	42.2
MEDIAN AUC(8-61d) [µg*days/g]	105.0	348.0
N	12	12

FIGURES 7 AND 8





CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-846

ADMINISTRATIVE DOCUMENTS